EDICAL LIBRARY

DEC 10 1947

VOLUME 74 NUMBER 4

AMERICAN JOURNAL

OF

DISEASES OF CHILDREN

EDITORIAL BOARD

CLIFFORD G. GRULEE, Chief Editor
Box 671, Evanston, Ill.

OSCAR M. SCHLOSS, New York
FRITZ B. TALBOT Boston
A. A. WERCH, Cincinnati
H. F. HELMHOLZ, Rochester, Minn.
FRANCIS SCOTT SMYTH, San Francisco
JAMES L. WILSON, Ann Arbor, Mich.

OCTOBER 1947

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

COPYRIGHT, 1947, BY THE AMERICAN MEDICAL ASSOCIATION

CONTENTS OF PREVIOUS NUMBER

SEPTEMBER 1947. NUMBER 3

Prevalence of Dental Caries in Malnourished Children: A Clinical Study. Howard Dyckes, D.D.S.; Arvie W. Moon, D.D.S.; Tom E. Sides, M.D., and Thelma A. Skinner, Birmingham, Ala.

Demonstration of Anti-Rh Antibody in Infants with Erythroblastosis Foetalis. Warren E. Wheeler, M.D., and Mary Louise L. Scheil, M.D., Columbus, Ohio.

Clinical Studies in Children with the Nephrotic Syndrome. Sidney P. Gottlieb, Ph.D.; John F. Steinmetz, M.D., and Benjamin Kramer, M.D., Brooklyn.

Porphyria and Porphyrinuria: Report of a Case; Review of Porphyria Metabolism with a Study of Congenital Porphyria. Irvin Dunphy, M.D., Cincinnati, and Smith Freeman, M.D., Ph.D., and Stanley Gibson, M.D., Chicago.

Hyperimmune Serums in Treatment of Whooping Cough: Clinical Results, with Notes on Pneumococcic Studies and Cutaneous Tests. Samuel L. Kahn, M.D., and Gisel Rosenthal, M.D., New York; Manfred Weichsel, M.D., Long Island City, N. Y., and Lillian Buxbaum, B.S.; Alfred E. Fischer, M.D.; Dorothea E. Godenker, M.D., and Catherine Ladyjensky, M.D., New York.

Case Reports:

Acetylsalicylic Acid Poisoning with Recovery. J. E. Gillespie, M.D., and R. R. Dubos, M.D., Urbana, Ill.

News and Comment.

Abstracts from Current Literature.

Society Transactions:

American Academy of Pediatrics.

Book Reviews.

Directory of Pediatric Societies.

American Journal of Diseases of Children

VOLUME 74 OCTOBER 1947 NUMBER 4

COPYRIGHT, 1947, BY THE AMERICAN MEDICAL ASSOCIATION

INFARCTION OF THE LUNG IN CHILDREN

ELLA ZUSCHLAG, M.D.
Fellow in Pediatrics, Mayo Foundation
ROCHESTER, MINN.

PULMONARY infarction is considered to be extremely rare in children. Although it does not occur frequently, it is encountered much oftener than is commonly believed. In this paper the relative frequency of pulmonary infarction in children and the conditions under which it may occur will be considered.

A review of the literature revealed that the first case of pulmonary infarction in a child was reported in 1833 [1] and that since that time reference has been made to at least 100 cases among children; 74 of these cases were reported in some detail. New data included here comprise material from 38 additional cases. Thirty-five of these cases were drawn from the records of the Mayo Clinic for 1910 to 1945, inclusive, and the other 3 cases were observed in the department of pathology, University of Minnesota, in 1941 and in 1944.

CONTROLLING FACTORS IN PULMONARY INFARCTION

The factors in the formation of a pulmonary infarct may be divided according to their physiologic, anatomic and pathologic characteristics.

It is an interesting observation that blood clotting, which in a great variety of circumstances is a distinctly protective process, should become detrimental to the animal mechanism in a few instances.[2] There has been a great deal of controversy concerning the clotting of blood, but most investigators now agree that the four factors outlined in Howell's [3] theory are responsible for it.

Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Pediatrics. Information relative to the additional cases has been added to the data in the thesis.

1. Billard, C. M.: A Treatise on the Diseases of Infants, Founded on Recent Clinical Observations and Investigations in Pathological Anatomy Made at the Hospice des Enfants-Trouvés, with a Dissertation on the Viability of the Child, translated from the French by J. Stewart, ed. 3, New York, George Adlard, 1839, p. 403.

2. MacCallum, W. G.: A Text-Book of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

3. Howell, W. H.: The Condition of the Blood in Hemophilia, Thrombosis and Purpura, Arch. Int. Med. **13**:76-95 (Jan.) 1914.

Embolism or thrombosis in the lung may result in varying degrees of infarction, depending on the location and the extent of the vascular occlusion. The distinctive anatomy of the lung must be well understood before a clear conception of this process can be obtained.[4]

It has been shown that it is almost impossible to produce infarction in the lung of a healthy animal by introducing bland emboli into the pulmonary circulation because nutrition in the region of the obstruction is supplied immediately by the adjacent branches of blood vessels. However, when pathologic changes occur in the lungs, as well as throughout the body, there is a strong possibility that pulmonary infarction will occur.[5]

It is generally agreed that several factors are responsible for thrombosis. There is clinical as well as experimental evidence that (1) endothelial injury,[6] (2) circulatory stasis,[7] (3) certain changes in the blood and (4) infection [8] may be combining factors in the pro-

---

4. Miller, W. S.: The Lung, Springfield, Ill., Charles C Thomas, Publisher, 1937.

5. (*a*) Hall, G. E., and Ettinger, G. H.: An Experimental Study of Pulmonary Embolism, Canad. M. A. J. **28**:357-368 (April) 1933. (*b*) Loeffler, L.: Pulmonary Embolism and Infarction, Arch. Path. **31**:93-98 (Jan.) 1941. (*c*) Mann, F. C.: Pulmonary Embolism: An Experimental Study, J. Exper. Med. **26**:387-393 (Sept.) 1917. (*d*) Nissen, R.: Der massive Lungenkollaps (mit experimentellen Untersuchungen über die Beziehungen von Atelektase und Lungenembolie), Arch. f. klin. Chir. **167**:567-581, 1931. (*e*) Van Allen, C. M.; Nocoll, G. L., and Tuttle, W. M.: Lung Changes After Occlusion of Pulmonary Artery Branches by Embolus and by Ligature, Yale J. Biol. & Med. **2**:363-389 (May) 1930. (*f*) Virchow, R.: Ueber die Verstopfung der Lungenarterie, in Gesammelte Abhandlungen zur wissenschaftlichen Medicin, Frankfurt am Main, Meidinger Sohn & Comp., 1856, pp. 221-226.

6. (*a*) Armentrout, A. W., cited by Rosenthal.[8i] (*b*) Aschoff, L.: Thrombosis, Arch. Int. Med. **12**:503-525 (Nov.) 1913.

7. (*a*) Aschoff.[6b] (*b*) Andral, G., cited by Rosenthal.[8i] (*c*) Billings, F. T.: Primary Thrombosis of the Pulmonary Artery, Pennsylvania M. J. **25**:152-161 (Dec.) 1921.

8. (*a*) Billings.[7c] (*b*) Barker, N. W.; Nygaard, K. K.; Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism: I. Incidence in Various Types of Operations, Proc. Staff Meet., Mayo Clin. **15**:769-773 (Dec. 4) 1940; (*c*) II. Predisposing Factors, ibid. **16**:1-5 (Jan. 2) 1941; (*d*) III. Time of Occurrence During the Postoperative Period, ibid. **16**:17-21 (Jan. 8) 1941; (*e*) IV. Location of Thrombosis: Relation of Thrombosis and Embolism, ibid. **16**:33-37 (Jan. 15) 1941. (*f*) Hirschboeck, J. S., and Coffey, W. L., Jr.: Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, Am. J. M. Sc. **205**:727-730 (May) 1943. (*g*) Hunter, J., cited by Rosenthal.[8i] (*h*) Lubarsch, O.: Thrombose und Infektion, Berl. klin. Wchnschr. **55**:225-229 (March 11) 1918. (*i*) Rosenthal, S. R.: Thrombosis and Fatal Pulmonary Embolism: Comparison of Their Frequency in the Clinics of Central Europe and North America with Special Reference to Increase, Arch. Path. **14**:215-237 (Aug.) 1932.

duction of thrombi. Venoclysis,[9] allergy,[10] changes in the weather,[11] atelectasis[12] and even adrenal insufficiency[13] have been proposed as additional causes. The following significant changes in the blood in the presence of infarction have been observed: anemia,[14] and increases in the carbon dioxide–combining power,[15] the calcium level,[16] the plasma fibrinogen[8f] and the number of platelets.[17] The extremely prominent role which infection plays in the production of pulmonary embolism and thrombosis has been stressed by many investigators.[18] Septic emboli, as shown by Virchow in 1856,[5f] may lead to extensive injury to the pulmonary tissues and readily cause infarction even when originally only small portions of lung were affected. From the present study, it is apparent that in cases of pulmonary infarction in children infection is the outstanding etiologic factor.

There is much disagreement in the literature concerning the etiology of thrombosis, and there is even more dissension over the differentiation of primary and embolic thrombosis. Belt[19] pointed out that in

9. (*a*) Friedrich, H., and Buchaly, J. F., cited by Rumold.[9c] (*b*) Orator, V., and Schleusing, H., cited by Rumold.[9c] (*c*) Rumold, M. J.: Experimental Pulmonary Embolism Associated with Venoclysis, Arch. Surg. **30**:685-701 (April) 1935. (*d*) Strauss, L., cited by Rumold.[9c]

10. Dietrich, A., and Schröder, K., cited by Rosenthal.[8i] Klemensiewicz, R., cited by Rosenthal.[8i] Knepper, R., and Waaler, G.: Hyperergische Arteriitis der Kranz- und Lungengefässe bei funktioneller Belastung, Virchows Arch. f. path. Anat. **294**:587-594, 1935. Miller, R. H., and Rogers, H., cited by Rosenthal.[8i] Turnbull, J. A.: Allergy as a Factor in Thrombosis, Am. J. Digest. Dis. **10**:184-188 (May) 1943.

11. Domrich, H.: Lungenembolie und Wetter, Deutsche Ztschr. f. Chir. **234**: 149-158, 1931. Domrich, H., and Wagemann, H.: Lungenembolie und Wetter, ibid. **238**:390-401, 1932. Fritzsche, E.: Witterung—Thrombose und Lungenembolie, Schweiz. med. Wchnschr. **60**:889-896 (Sept. 20) 1930.

12. (*a*) Castleman, B.: Pulmonary Infarction and Atelectasis: Report of a Case Presenting Evidence of a Causal Relationship, Arch. Path. **35**:299-303 (Feb.) 1943. (*b*) de Takats, G.; Fenn, G. K., and Jenkinson, E. L.: Reflex Pulmonary Atelectasis, J. A. M. A. **120**:686-690 (Oct. 31) 1942. (*c*) Nissen.[5d]

13. Scott, W. J. M., and Thatcher, H. S.: Pulmonary Emboli in Suprarenal Insufficiency, Arch. Path. **2**:806-814 (Dec.) 1926.

14. Barker and associates.[8b,e] Hirschboeck and Coffey.[8f]

15. (*a*) Binger, C. A. L., and Moore, R. L.: Changes in Carbon Dioxide Tension and Hydrogen Ion Concentration of the Blood Following Multiple Pulmonary Embolism, J. Exper. Med. **45**:633-641 (April) 1927. (*b*) Friedemann, M., cited by Rosenthal.[8i] (*c*) Prima, C., cited by Rosenthal.[8i]

16. Rosenthal.[8i] Gechtman, G. Y., and Slauskayu, cited by Rosenthal.[8i]

17. Hirschboeck and Coffey.[8f] Prima.[15c]

18. Hunter.[8g] Lubarsch.[8h] Møller, P.: Studien über embolische und autochthone Thrombose in der Arteria pulmonalis, Beitr. z. path. Anat. u. z. allg. Path. **71**:27-77, 1923.

19. Belt, T. H.: The Aetiology of Lung Infarction, Brit. Heart J. **1**:283-289 (Oct.) 1939.

order to make the distinction between thrombus and embolus the entire obstructing clot must be exposed satisfactorily. Accomplishment of this exposure, he stated, requires a technic of dissection that will permit opening of the second, third and even fourth divisions of the pulmonary arteries without undue mutilation of the lungs. In addition to the detailed gross dissection, he emphasized the necessity of making serial sections in order to carry out adequate microscopic studies of the changes in the wall of the blood vessel itself. Even after microscopic study has been made, accurate interpretation of the observations is obviously essential. As an example, Belt [20] noted the involutional change in a vessel wall beyond the point of embolic occlusion as being similar to that seen in the umbilical artery after birth. Such involutional changes may be mistaken for endarteritis because of the usually associated proliferative changes in the intima.

EFFECTS OF PULMONARY THROMBOSIS OR EMBOLISM

In cases of occlusion of the pulmonary artery changes occur in the circulation,[21] the pulmonary tissues,[22] the blood chemistry [15a] and the vagal tone (bronchial spasm).[23] The incidence and severity of these effects are dependent on the location, the extent and the rapidity of the obstruction to the blood flow,[24] as well as on the condition of the patient.[21b] The more gradual the occlusion of the pulmonary artery or its branches, the less is the cross sectional area of the vessel required to maintain life.[25] Similarly, occlusion of the smaller arteries will not be manifested by immediate clinical effects unless there is widespread occlusion,[5a] or unless the lesions are accompanied with a debilitating

20. Belt, T. H.: Autopsy Incidence of Pulmonary Embolism, Lancet **1**:1259-1260 (June 3) 1939.

21. (*a*) Loeffler.[5b] (*b*) Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:1189-1241 (Dec.) 1935. (*c*) Gibbon, J. H.; Hopkinson M., and Churchill, E. D.: Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, J. Clin. Investigation **11**: 543-553 (May) 1932. (*d*) Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, Arch. Surg. **6**:764-783 (May) 1923.

22. (*a*) Hall and Ettinger.[5a] (*b*) Van Allen and others.[5e] (*c*) Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings, with Special Reference to Pulmonary Embolism and Infarction, Am. J. Roentgenol. **43**:305-326 (March) 1940.

23. de Takats and others.[12b] Jesser, J. H., and de Takats, G.: The Bronchial Factor in Pulmonary Embolism, Surgery **12**:541-552 (Oct.) 1942.

24. Hall and Ettinger.[5a] Loeffler.[5b] Gibbon and others.[21c] Haggart and Walker.[21d]

25. Gibbon and others.[21c] Haggart and Walker.[21d]

condition in the patient.[26] It is believed that instances of occlusion of the smaller pulmonary branches would be discovered more frequently if more sections were taken from the lung at necropsy.[21b]

MECHANISM OF DEATH IN OCCLUSION OF THE PULMONARY ARTERY

In spite of the many detailed descriptions of the various changes occurring throughout the body, as well as in the cardiorespiratory system, the exact mechanism of death resulting from occlusion of the pulmonary circulation is still a subject of much controversy.

The neurogenic theory maintains that death in the presence of occlusion of the pulmonary circulation is due to a reflex cardiac standstill, to inhibition of the respiratory center or to vasomotor shock, or to all three. Reflex pulmonary atelectasis may act subsequently as an additional mechanical factor in producing respiratory distress.[27] In the opinion of Barnes,[28] it is possible, "if sympathetic reflexes are important in the production of the total chain of serious events, that reflex spasm of some or all of the pulmonary arteries at the hilus may be at least one part of the dangerous reflex mechanism."

Mechanical factors in the production of death from occlusion of the pulmonary artery affect both the cardiac and the respiratory system.[29] Obstruction of the pulmonary circulation results in reduced cardiac output, cerebral anemia and pulmonary congestion due to the increased venous pressure. A mechanical factor may be the initial one, but undoubtedly there is a combination of factors before death ensues.[28]

CLINICAL OBSERVATIONS

The clinical diagnosis of pulmonary infarction has been rarely made in children. This does not necessarily reflect any discredit on the clinician, since the coexisting disease may have a masking effect. Realizing that pulmonary infarction in children is not a totally unexpected occurrence, the clinician must learn to interpret the signs and symptoms of this condition as it occurs in children of the younger age groups.

The sudden onset of cyanosis, pallor, dyspnea, weakness, apprehension or restlessness, rapid or irregular respiration, rapid and thready pulse, irregular cardiac rate and rhythm, fall in blood pressure, profuse

26. Pilcher, R.: Pulmonary Embolism: A Statistical Investigation of Its Incidence in Twelve London Hospitals in the Decade 1925-1934, Brit. J. Surg. **25**:42-56 (July) 1937.

27. de Takats and others.[12b] Gosset, A.; Bertrand, I., and Patel, J.: Sur la physio-pathologie des embolies artérielles des membres (récherches expérimentales), Ann. d'anat. path. **9**:841-862 (Nov.) 1932.

28. Barnes, A. R.: Pulmonary Embolism, J. A. M. A. **109**:1347-1353 (Oct. 23) 1937.

29. Pilcher, R.: The Rôle of Obstruction in Fatal Pulmonary Embolism, Lancet **1**:1257-1258 (June 3) 1939.

perspiration, hemoptysis, pain in the chest and extreme prostration constitutes the usual picture of pulmonary embolism. In cases in which a large embolus lodges in one of the main pulmonary arteries, the picture of sudden disaster which usually appears in adults may be seen in children, but an onset of this type is rare. There is usually, instead, a change in the general condition, which during the ensuing days may improve temporarily or may even become progressively worse as the infarction becomes more extensive. The clinical picture may eventually resemble that of pneumonia: short, shallow, painful respirations; dry, nonproductive cough, or sometimes bloody sputum, weak pulse and cyanosis.

Gerhardt,[30] in 1878, gave the earliest and most complete description of pulmonary infarction in children. He stated that at first the physical signs may consist of coarse rales. After a few days, dulness on percussion, increased vocal fremitus and bronchial breathing may be detected. Pleurisy with the characteristic friction rub or with pain may be present. Pneumothorax may result in some instances. According to several more recent observers[31] who studied pulmonary infarction in the older age groups, there may be no early signs of pulmonary involvement. However, signs of pulmonary congestion may soon develop in the opposite lung or in other lobes of the affected lung.[31c] The complete or incomplete consolidation of pulmonary infarction on the involved side will be observed later if venous return is impeded. Limited expansion on the affected side and pleurisy with a friction rub also may be encountered.[32] In cases of massive pulmonary embolism which is not fatal, increased cardiac dulness due to dilatation of the right ventricle and pulmonary conus may be evident.[31a] Murnaghan, McGinn and White[33] observed increased pulsation in the second and third interspaces to the left of the sternum, with a loud systolic murmur in this region, accentuation of the pulmonic second sound and, at times, a friction rub. Occasionally, gallop rhythm is present. The veins of the neck frequently are engorged and pulsating.[31a]

---

30. Gerhardt, C.: Der hämorrhagische Infarct, in Hennig, C., and others: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1878, vol. 3, pt. 2, pp. 823-830.

31. (*a*) Crawford, B. L., and Mohler, H. K.: A Clinical and Pathologic Study of Acute Pulmonary Embolism and Thrombosis, Pennsylvania M. J. **40**: 1020-1026 (Sept.) 1937. (*b*) Graves, W. N.: Pulmonary Embolism: A Statistical Review of Cases From 1929 Through 1938, Surg., Gynec. & Obst. **70**:958-963 (May) 1940. (*c*) Robertson, H.: A Clinical Study of Pulmonary Embolism: An Analysis of One Hundred and Forty-Six Fatal Cases, Am. J. Surg. **41**: 3-21 (July) 1938.

32. Crawford and Mohler.[31a] Graves.[31b]

33. Murnaghan, D.; McGinn, S., and White, P. D.: Pulmonary Embolism With and Without Acute Cor Pulmonale, with Special Reference to the Electrocardiogram, Am. Heart J. **25**:573-597 (May) 1943.

In cases of pulmonary infarction in children associated with infections, the incorrect diagnosis of pneumonia, or of atelectasis, may frequently be made because of the similar physical and clinical manifestations. This error is especially likely to be made whenever gradual progression of the pulmonary infarctions result from multiple small thrombi or emboli.

The roentgenologic findings in cases of pulmonary infarction are not as characteristic in many instances as is generally believed.[34] Hampton and Castleman [22c] stated that "the roentgen shadow of an early infarct does not usually develop before twelve hours and occasionally not before twenty-four hours after onset of symptoms." The usual fan-shaped area of consolidation need not be present, since "the shape of the infarct is dependent entirely upon the shape of the part of the lung it involves," and since atelectasis, edema and pneumonia are such frequent coexisting lesions. "Round shadows, which one does not usually associate with infarction, may be produced by two or more infarcts if projected in the proper direction." Accentuation of the hilar shadow on the side of the vascular occlusion and pleural effusion have been observed by many roentgenologists [35] in cases of pulmonary embolism. The hilar shadow is said to be due to dilatation of the pulmonary vessels on the affected side and is believed to be early roentgenologic evidence of occlusion of pulmonary vessels.[35]

Characteristic electrocardiographic changes have been shown by Barnes [36] and others [33] to occur in cases of pulmonary embolism or infarction. While electrocardiography is a valuable diagnostic procedure in adults, it is impossible to appraise its value in the diagnosis of pulmonary infarction in children, since the method has not been used in a sufficient number of cases.

In general, the clinical signs of pulmonary infarction among children are not characteristic and are not as clearly developed as in adults; consequently, atelectasis, pneumonia and pulmonary infarction cannot always be distinguished.

CASES IN THE LITERATURE

Although references to at least 100 cases of pulmonary infarction in children have been made in the literature, only 74 cases were reported in any detail. A table giving the details in most of these cases is included in my thesis on this subject.[37] It is significant that in nearly

34. Castleman, B.: Healed Pulmonary Infarcts, Arch. Path. **30**:130-142 (July) 1940.

35. Pugh, D. G.: Personal communication to the author.

36. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**:11-13 (Jan. 2) 1936.

37. Zuschlag, E.: Pulmonary Infarction in Children, Thesis, Graduate School of the University of Minnesota, 1945.

every case infarction of the lung accompanied infection or a cachectic state. In 28 cases (41.8 per cent) pneumonia was observed[38]; in 15 of these cases measles was a further complication.[39] In addition, in 9 cases pulmonary infarction was associated with sinus thromboses[40]; in 8, with otitis media[41]; in 8, with cardiac disease[42]; in 7, with patent

38. (*a*) Bull, P.: What Can More Than Six Thousand Post Mortem Examinations Teach Us About Emboli and Embolic Gangrene of the Extremities? Acta chir. Scandinav. **54**:315-338 (Jan.) 1922. (*b*) Dickinson, L.: Thrombosis of the Pulmonary Artery in a Case of Congenital Stenosis of the Orifice, Tr. Path. Soc. London **48**:57-58, 1897. (*c*) Fleischmann, R.: Embolie der Arteria pulmonalis bei Masern, Ztschr. f. Kreislaufforsch. **21**:377-385 (July 1) 1929. (*d*) Gehrt: Thrombose der Arteria pulmonalis im Kindesalter, Ztschr. f. Kinderh. **36**:221-228, 1923. (*e*) Graf, G.: Infarto emorragico di un lobo azigos polmonare in un neonato di tre settimane, portatore di una complessa cardiopatia congenita (transposizione corretta dei grossi vasi, pervietà dei setti interventricolare ed interatriale), Pediatria **46**:740-751 (Aug.) 1938. (*f*) Gunter, J. U.: Thrombosis of the Pulmonary Artery in Identical Twins: Report of Cases with Autopsy, Arch. Path. **31**:211-214 (Feb.) 1941. (*g*) Halff, J., cited by Lutz.[38l] (*h*) Lasker, A. E., cited by Lutz.[38l] (*i*) Lutz, W.: Ueber Thrombenbildung bei Masern, mit besonderer Beteiligung der Lungenarterien, Berl. klin. Wchnschr. **50**:1566-1570 (Aug. 25) 1913. (*j*) Mori Chavez, P.: Thrombosis progresive obliterante de la arteria pulmonar, Rev. peruana de pediat. **1**:98-105 (Dec.) 1942. (*k*) Robin, A.: Physiologie pathologique d'un cas de gangrène du poumon, avec oblitération de l'artère pulmonaire, chez un enfant atteint de rougeole et de broncho-pneumonie consecutive, Bull. Soc. anat. de Paris **50**:522-530 (July) 1875. (*l*) Rupp, A.: Postoperativ Thrombose und Lungenembolie, Arch. f. klin. Chir. **115**:672-690, 1921. (*m*) Wessen, N.: Tötliche Lungenembolie bei einem vier jährigen Kind nach Rippenresektion bei Pleuraempyem, Acta chir. Scandinav. **54**: 123-131, 1921-1922.

39. (*a*) Fleischmann.[38c] (*b*) Gehrt.[38d] (*c*) Halff.[38g] (*d*) Lutz.[38l] (*e*) Robin.[38k] (*f*) Guillemot, L.: Gangrène pulmonaire otogène chez un nourrisson de sept mois, Bull. Soc. de pédiat. de Paris **8**:229-234, 1906; abstracted, Arch. de méd. d. enf. **9**:383, 1906.

40. (*a*) Fleischmann.[38c] (*b*) Halff.[38g] (*c*) Lutz.[38l] (*d*) Langenbeck, cited by Gerhardt.[30] (*e*) Löschner: Pylephlebitis-Höhgradiger Icterus: Ecchymosen an der Lungenpleura mit Infarctus in einzelnen Lungenparthien; Alte Bronchialdrüsentuberculose; Darmhämorrhagie, Jahrb. f. Kinderh. **2**:140-142, 1859. (*f*) Pehu, M. M., and Horand, R.: Gangrène pulmonaire embolique otogène chez un enfant de six ans, Lyon méd. **104**:1307-1313, 1905.

41. (*a*) Gunter.[38f] (*b*) Lutz.[38l] (*c*) Guillemot.[39f] (*d*) Pehu and Horand.[40f] (*e*) Jones, J. A.: Pulmonary Embolism in an Infant Following Aural Infection, Lancet **2**:1070-1071 (Nov. 15) 1930. (*f*) Schlaepfer, K.: Chronic and Acute Arteritis of the Pulmonary Artery and of the Patent Ductus Arteriosus, Arch. Int. Med. **37**:473-488 (April) 1926.

42. (*a*) Dickinson.[38b] (*b*) Graf.[38e] (*c*) Gordon, H., and Perla, D.: Subacute Bacterial Endarteritis of Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonic Stenosis, Am. J. Dis. Child. **41**:98-109 (Jan.) 1931. (*d*) Löschner: Klinische Fälle aus dem Franz-Josef-Kinderspitale in Prague: II. Phlebitis venae cruralis sinistrae, Peri-et Myocarditis, Embolia et Oedema pulmonum,

ductus arteriosus,[43] and in 3, with thromboses in peripheral veins.[44] Other conditions in which pulmonary infarctions were encountered were: meningitis [40f]; mastoidtitis [45]; pleural empyema [46]; influenza ("grip") [38d]; diphtheria [47]; osteomyelitis [44c]; suppurative arthritis [38a]; nephritis [38c]; nephrosis [48]; pertussis [38j]; generalized tuberculosis [21b]; typhoid [49]; gastroenteritis [50]; phlebitis of the umbilical cord [51]; cephalhematoma [52]; abscess of the liver [42d]; bacterial endocarditis [53]; bacteremia (Staphylococcus aureus,[54] Streptococcus viridans,[41f] influenza bacil-

Jahrb. f. Kinderh. **4**:66-69, 1861. (*e*) Pasteur, W.: Fatal Pulmonary Apoplexy (Probably Embolic) in an Apparently Healthy Girl Aged Fourteen Years, Lancet **1**: 475-476 (Feb. 22) 1896. (*f*) Prettin, F.: Thrombose und tödliche Lungenembolie, Virchows Arch. f. path. Anat. **297**:535-543 (Aug.) 1936. (*g*) Smellie, J. M.: Pulmonary Embolism in Childhood, Arch. Dis. Childhood **4**:328-329 (Oct.) 1929. (*h*) Whipham, T. R.: A Heart Showing an Infective Polypoid Thrombus in the Pulmonary Artery and Extending into the Right Ventricle, Mistaken for Patent Ductus Arteriosus, Proc. Roy. Soc. Med. (pt. 1) **4**:199-201, 1911.

43. (*a*) Schlaepfer.[41f] (*b*) Bettinger, H.: Beiträge zur Pathologie des Ductus Botalli, Centralbl. f. allg. Path. u. path. Anat. **54**:289-295 (May 20) 1932. (*c*) Gross, R. E.: Arterial Embolism and Thrombosis in Infancy, Am. J. Dis. Child. **70**:61-73 (Aug.) 1945. (*d*) Rauchfuss, C.: Ein Fall von Verstopfung der Lungenarterien eines vier Wochen alten Kindes, Virchows Arch. f. path. Anat. **17**:474-479, 1859. (*e*) Schlagenhaufer, F.: Ein Fall von Influenze-Endocarditis der Aortenklappen und des offenen Ductus Botalli, Ztschr. f. Heilk. **22**:19-28, 1901. (*f*) Wagener, O.: Thrombenbildung am durchgängigen Ductus arteriosus (Botalli), Deutsches Arch. f. klin. Med. **89**:626-631, 1907.

44. (*a*) Fleischmann.[38e] (*b*) Löschner.[42d] (*c*) Curtin, R. G.: Pulmonary Hemorrhagic Infarction in a Child, Following a Slight Injury to the Leg, Am. J. Obst. & Gynec. **11**:611-612 (July) 1878.

45. Gunter.[38f] Guillemot.[39f] Pehu and Horand.[40f] Jones.[41e]

46. Lasker.[38h] Wessen.[38m]

47. Gehrt.[38d] Prettin.[42f] Weickert: Diphtheritis und Pneumonia hämorrhagica bei einem siebentage alten Kind, Jahrb. f. Kinderh. **3**:332-334, 1870.

48. Mayner, F.: Death from Transfusion of Plasma, J. A. M. A. **116**:2015-2016 (May 3) 1941.

49. Weill, E.: Précis de médecine infantile, ed. 2, Paris, O. Doin, 1905, pp. 622-626.

50. (*a*) Billard.[1] (*b*) Gunter.[38f] (*c*) Rauchfuss.[43d] (*d*) Wagener.[43f] (*e*) Weill.[49] (*f*) Bednar, cited by Gerhardt.[30] (*g*) Hutinel, V.: Les maladies des enfants, Paris, Asselin & Houzeau, 1909, vol. 4, pp. 257-263. (*h*) Stulik, C. K., and Rust, B. K.: Pulmonary Embolism in Infancy, Am. J. Dis. Child. **37**:1246-1250 (June) 1929.

51. (*a*) Rauchfuss.[43d] (*b*) Bednar.[50f] (*c*) Köstlin, cited by Gerhardt.[30]

52. Bednar.[50f] Köstlin.[51c]

53. Rupp.[38l] Gordon and Perla.[42c] Whipham.[42h] Schlagenhaufer.[43e] Henning, cited by Gerhardt.[30]

54. Hosoi, K.: Pulmonary Embolism and Infarction: Analysis of Sixty-Four Verified Cases, Ann. Surg. **95**:67-92 (Jan.) 1932.

lus [43e]; smallpox [55]; blepharitis [43d]; transfusion of plasma [48]; injury [56]; thrombi in the sinuses,[57] cardiac auricles [58] or ventricles [59] or in a patent ductus arteriosus [43]; tracheobronchitis [60]; peritonitis,[31c] and "suffocation." [1]

Several statistical reviews of cases of pulmonary infarction seen at necropsy have included several among children but have failed to give sufficient detail to justify inclusion of such cases in this study.[61]

Many of the observations reported in the literature concerning pulmonary infarction in all age groups indicated that the right lung, especially the lower lobe, was more frequently involved than the left lung. Schultz,[62] in 1924, applied this statement to the occurrence of pulmonary infarctions in children. This conclusion cannot be substantiated, however, by the data available in the 74 cases reviewed in the present study. In this series, the location of the infarcts was given in 52 cases; and of the latter, the infarcts were in both lungs in 25 cases, in the left lung in 14 cases and in the right lung in 13 cases.

In the cases reviewed in the literature, embolism was probably the commonest cause of the pulmonary infarcts. Gerhardt,[30] in 1878, stated that marantic thrombi in infants occurred chiefly in cases of severe diarrhea with cachexia. The original sites of the thrombi in children differed from those in adults, in whom the origin was in the veins of the lower extremities and the pelvis (uterus and prostate gland), whereas in children the origin was from thrombi in the cerebral sinuses or the renal veins. He expressed the opinion that this difference was explained by the fact that the veins of the lower extremities in many adults become increasingly dilated, and that since the genital organs

55. (*a*) Barrier, cited by Gerhardt.[30] (*b*) Rilliet and Barthez, cited by Gerhardt.[30]

56. (*a*) Pilcher.[26] (*b*) Curtin.[44c] (*c*) Rosenbloom, H., and Henderson, R. J.: Pulmonary Infarct in a Child, Brit. M. J. **2**:64 (July 13) 1935.

57. Rauchfuss and Reimer, cited by Gerhardt.[30]

58. Bull.[38a] Graf.[38e] Smellie.[42g]

59. Bull.[38a] Lutz.[38l] Rosenbloom and Henderson.[56c]

60. Guinon, L.: Thrombose double de l'artère pulmonaire, Bull. Soc. de pédiat. de Paris **3**:191-193, 1901.

61. Breslich, P. J.: Pulmonary Embolism: A Report of Fifty Four Cases, Journal-Lancet **58**:445-499 (Oct.) 1938. Collins, D. C.: Pulmonary Embolism Based upon a Study of Two Hundred and Seventy One Instances, Am. J. Surg. **33**:210-219 (Aug.) 1936. Sarafoff, D.: Statistik über das Vorkommen von Thrombosen und Lungenembolien an der Leipziger Chirurg Universität Klinik für das Dezennium 1920 bis 1929, Arch f. klin. Chir. **161**:493-501, 1930. Westdahl, P. R.: Pulmonary Embolism: A Review of the Literature with Additional Statistics Gathered from a Study of Two Hundred and Forty Seven Cases, West. J. Surg. **49**:77-83 (Feb.) 1941.

62. Schultz, O. T., in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 4, chap. 65, pp. 33-59.

are not developed in children the pelvic veins do not show the dilatation seen in the pelvic veins of adults. Gerhardt stated that thrombi might be primary in the pulmonary vessels in cases in which there was compression of the lungs and their vessels by elevation of the diaphragm, by intrathoracic tumors, or even by intra-abdominal conditions. He also stated that numerous whitish red infarcts might occur in children with leukemia as a result of plugging of pulmonary vessels with white blood cells. Since the report of Rauchfuss,[43d] in 1859, several cases have been reported in which thrombi developed in the patent ductus arteriosus, some in the absence of coexisting infections, and in several instances pulmonary infarction resulted.[48] Lutz [381] called attention to the relative frequency with which thrombosis of the pulmonary artery was a complication of measles in very young children.

In only 24 of the cases of pulmonary infarction reported in the literature was reference made to thrombi in other parts of the body. Their locations were as follows: intracranial venous sinuses, in 9 cases; cavities of the heart, in 7 cases; patent ductus arteriosus, in 7 cases, and peripheral veins, in 3 cases. Thrombi were present in more than one location outside the lungs in several of these cases.

The symptoms and signs of pulmonary infarction were described briefly in only 39 of the 74 cases reported in detail in the literature. In 10 of these 39 cases there was an acute onset of the terminal event, either sudden death or sudden change in the general condition followed by a progressive decline. In the remaining 29 cases there was a gradual progression of the symptoms, which were predominantly those of the underlying disease.

NEW CASES STUDIED

Thirty-eight cases of pulmonary infarction in children not previously reported in the literature were studied. A review of the records of children less than 15 years of age who came to the Mayo Clinic from 1910 to 1945, inclusive, revealed 32 cases in which pulmonary infarction was seen at necropsy and 3 cases in which there was clinical evidence of the condition. The 32 cases in which pulmonary infarctions were seen post mortem represent 2.13 per cent of the total number of necropsies performed on children less than 15 years of age during this period. Three additional cases were observed at necropsy in this age group in the department of pathology of the University of Minnesota; of these, I saw 2 in 1941, and the other case was observed by Dr. Alexander M. Iams in 1944.

The conditions under which pulmonary infarcts were observed in children in this series of cases are given in table 1, in the order of frequency in which they occurred.

Pulmonary infarction followed surgical procedures in 16 (42.1 per cent) of the 38 cases. It occurred from one hour to thirty-seven days

after operation, or an average of 9.39 days. The types of operative procedures are enumerated in table 2.

In 32 cases (84.2 per cent) the pulmonary infarction was associated with infection (figs. 1, 2 and 3 *a*). In 14 of these 32 cases (46.7 per cent) an infection of the blood stream was demonstrated.

In 13 (34.2 per cent) of the 38 cases coexisting infections of the lungs were demonstrated at necropsy. In these 13 cases, there were 1 case of tuberculosis, 1 case of periarteritis nodosa associated with changes in the pulmonary vessels and 11 cases of pneumonia, 2 of which were complicated with empyema.

TABLE 1.—*Conditions Under Which Pulmonary Infarction Occurred in Thirty-Eight Children*

Disease	No. of Cases
Bacteremia	14
Pneumonia	9
Acute osteomyelitis or arthritis (figs. 2 and 6)	6
Generalized or localized peritonitis (figs. 3*a* and 5)	6
Rheumatic pancarditis, with decompensation in 3 cases (fig. 3*b*)	5
Pleural empyema	4
Intracranial tumors	3
Nephritis	3
Congenital heart disease with endocarditis (fig. 1*a*)	2
Acute lymphatic leukemia; cardiac decompensation in 1 case (fig. 4)	2
Acute otitis media (fig. 1*b*)	2
Pericarditis; bacteremia in 1, pneumonia in 1	2
Meningitis	1
Omphalophlebitis	1
Pertussis with bronchopneumonia	1
Chronic ulcerative colitis	1
Cardiorenal disease (decompensated)	1
Generalized tuberculosis	1
Generalized periarteritis nodosa	1
Multiple abscess of liver	1
Infection of urinary tract	1
Laryngeal diphtheria	1
Gangrenous intestine with intestinal obstruction	1
Phenol poisoning with cellulitis of neck	1
Cleft palate (plastic repair) with cardiac hypertrophy	1

The 6 cases (15.8 per cent) of pulmonary infarction not associated with infection consisted of 2 cases of leukemia (fig. 4) and 4 cases of postoperative infarction. Of the latter, the infarction followed operations for intracranial tumors in 3 cases and the plastic repair of a cleft palate in 1 case.

There were 12 cases (31.5 per cent) of pulmonary infarction associated with heart disease (figs. 1 *a* and 3 *b*). In 5 of these cases (13.1 per cent) decompensation was present.

In most cases of this series (45.7 per cent) pulmonary infarction was observed to be multiple and to involve both lungs. The right lung was involved next most frequently (34.3 per cent), with a greater tendency for infarction to occur in the lower lobes.

Although no attempt was made to distinguish between pulmonary infarctions resulting from emboli and those due to thrombi, it was

interesting to observe that pulmonary infarction was associated with thrombus formation in other parts of the body. Thrombi were encountered in the femoral vein in 4 cases, the iliac vein in 4 cases, the longitudinal sinus in 2 cases, the lateral sinus in 2 cases, and in the renal, cerebral and hepatic veins, vena cava, right auricle and right ventricle in 1 case each.

TABLE 2.—*Pulmonary Infarction Occurring After Operation in Children Seen at the Mayo Clinic*

Case	Associated Disease	Operative Procedure	Interval After Operation, Days
1	Otitis media; bronchopneumonia; thrombosis of superior longitudinal and left lateral sinuses	Decompression of left temporal area	11
2	Intestinal obstruction; gangrene in loops of ileum; bilateral bronchopneumonia	Enterostomy	1
3	Pneumonia with empyema on left side; secondary anemia	Thoracoplasty	2½
4	Tumor of brain (astrocytoma)...	Ventriculography	3
5	Generalized tuberculosis; pelvic peritonitis with abscess	Drainage of pelvic abscess .	13
6	Catarrhal appendicitis; pneumonia; pericarditis; acute nephritis	Appendectomy	4
7	Multiple abscesses of liver and cervical region; staphylococcic and streptococcic (hemolytic) bacteremia; secondary anemia	Abdominal exploration and aspiration of abscesses of liver; drainage of cervical abscesses	26
8	Tumor of brain (astrocytoma)...	Bilateral cerebellar exploration with subtotal resection of cerebellar tumor	2
9	Gangrenous appendicitis with peritonitis; bilateral pleural empyema; streptococcic (hemolytic) bacteremia	Drainage of appendical abscess	10
10	Acute osteomyelitis of right femur; staphylococcic bacteremia	Drainage of abscess of right femur	20
11	Acute osteomyelitis of left femur; bacteremia due to Staph. aureus	Drainage of abscess of left femur	5
12	Acute arthritis of right hip; bacteremia due to Staph. aureus; pericarditis	Drainage of abscess of right femur	9
13	Cleft palate; cardiac hypertrophy; anemia	Plastic repair of cleft palate	1 hr.
14	Postappendectomy (elsewhere); abdominal abscesses	Abdominal exploration and drainage of abscess	37
15	Imperforate anus with colostomy; rectovaginal fistula; peritonitis following plastic repair	Closure of colostomy with plastic repair of rectovaginal fistula	7
16	Intracranial and intraorbital; neurofibroma	Craniotomy with removal of tumor	2

Information concerning the nature of the terminal symptoms was available in 34 of the 38 cases. Sudden death occurred in 9 (26.4 per cent) of the 34 cases. There was a gradual progression of symptoms in the remaining 25 cases.

Records of the symptoms and signs could be obtained in only 24 cases. Of these, changes in respiration and in the pulse were noted most

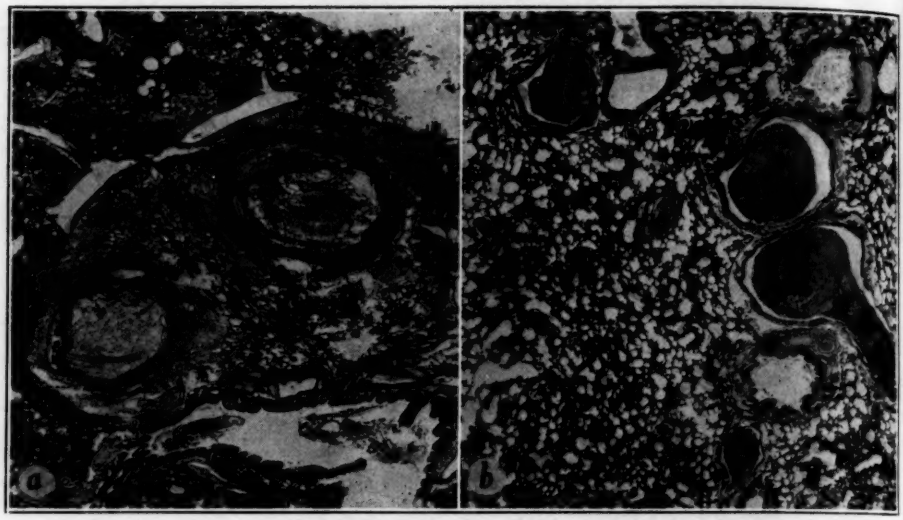


Fig. 1.—(*a*) Cross section from the lower lobe of the right lung, showing thrombi in the pulmonary arteries of a boy 5 years of age who had congenital heart disease associated with acute bacterial endocarditis; × 10. (*b*) Cross section through the lower lobe of the right lung, showing recent thrombi in the pulmonary arteries of a boy 7 months of age who died suddenly during an illness of bronchopneumonia and otitis media; × 13.

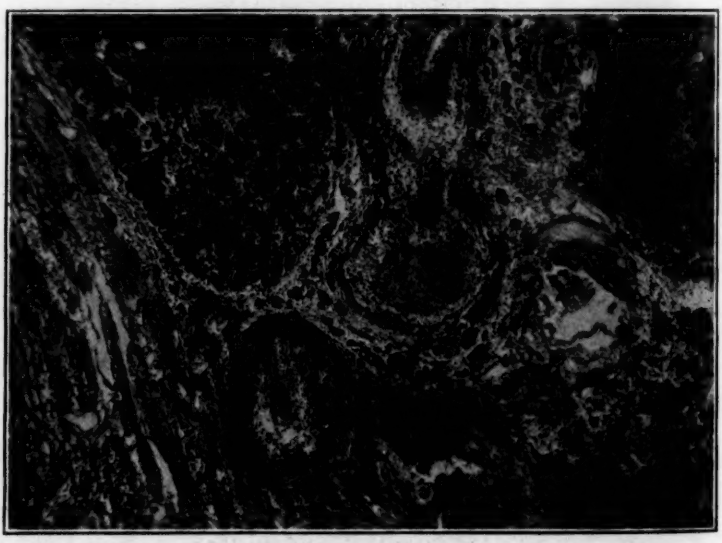


Fig. 2.—Cross section through the lower lobe of the left lung of a girl 12 years old who had acute osteomyelitis with bacteremia; a thrombus (probably of embolic origin) and beginning destruction of the wall of the artery may be noted. A portion of the abscess, containing organisms, is shown in the upper right hand corner; × 18.

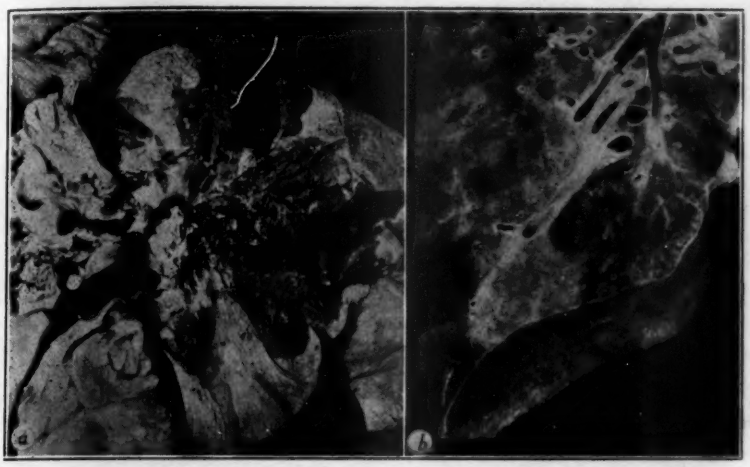


Fig. 3.—(*a*) Portion of the heart and lungs of a girl 5 years old who died of peritonitis following closure of colostomy; there is a thrombus in the left main pulmonary branch. (*b*) Cut surface of the lower lobe of the right lung of a girl 10 years old who died suddenly during an illness of rheumatic pancarditis with cardiac decompensation; a branching thrombus may be seen in the pulmonary arteries.

Fig. 4.—Portion of the lower lobe of the left lung of a girl 14 years old who had acute lymphatic leukemia; a large white thrombus is present in the left pulmonary artery.

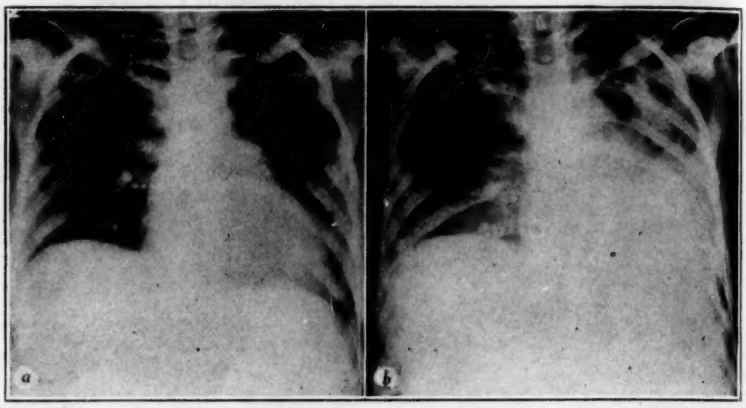


Fig. 5.—(*a*) Roentgenogram (Jan. 18, 1943, before pulmonary sypmtoms developed) of the chest of a girl 12 years old who had intra-abdominal abscesses following appendectomy. The azygous lobe should be noted. (*b*) Roentgenogram of the same patient on Feb. 10, 1943, five hours after the onset of symptoms strongly suggesting pulmonary embolism. The patient died after subsequent similar episodes.

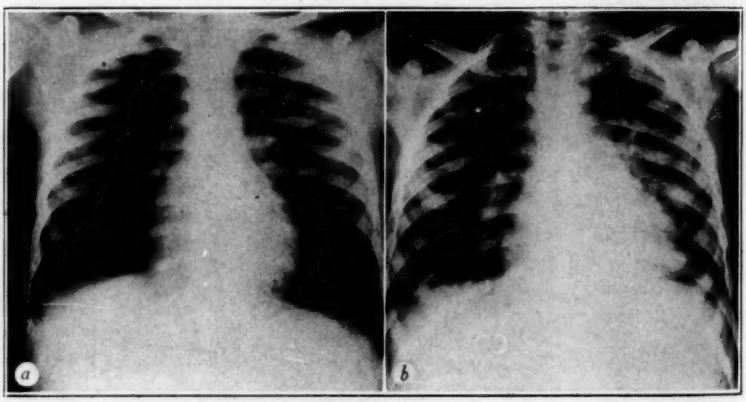


Fig. 6.—Roentgenograms of a boy 10 years old who had acute osteomyelitis and bacteremia due to Staph. aureus. (*a*) Normal roentgenogram made on July 28, 1937; (*b*) roentgenogram on August 17, one day before death. Diffuse infiltration in both pulmonary fields was interpreted as being due to metastatic lesions (infected emboli). The patient had a slight cough and minimal clinical signs in the chest. Necropsy revealed multiple infected pulmonary infarcts.

frequently. Respiratory distress or increased respiratory rate was observed in 13 cases, and increased pulse rate or a very feeble pulse was noted in 12 cases. Cyanosis was described in 9 and cough in 8 cases. Other symptoms and signs, in the order of the frequency recorded, were: unconsciousness, pallor, expectoration of bloody sputum, restlessness, apprehension, pain in the chest, "tightness in the chest," profuse perspiration, emesis, fall in blood pressure, engorged vessels of the neck and "collapse."

Ages of the patients at the time of registration at the hospital ranged from 9 days to 14 years. The age distribution was as follows: less than 1 month, 1 case; 1 to 6 months, 2 cases; 7 months to 1 year, 2 cases; 1 to 5 years, 10 cases; 6 to 10 years, 9 cases, and 11 to 14 years, inclusive, 14 cases.

There is apparently no significant difference in sex incidence in the cases of pulmonary infarction observed in children. Seventeen boys and 21 girls were affected.

In the 38 cases reviewed, roentgenograms of the chest usually did not serve to establish the diagnosis of pulmonary infarction. In most instances the clinical, as well as the roentgenographic, findings were compatible with the presence of the coexisting pulmonary disease, and infarction was not suspected. If infarction had been suspected, perhaps roentgenograms of the chest made at intervals would have been helpful in establishing this diagnosis (figs. 5 *a* and *b* and 6 *a* and *b*).

SUMMARY

Pulmonary infarctions occur more frequently in children than is generally believed. At least 74 cases are described in detail in the literature, and data on an additional 38 cases are reported in this paper.

The etiologic factors in thrombosis are endothelial injury, slowing of the blood flow and changes in the blood. Infection, atelectasis, allergy and venoclysis may be contributory factors.

The effects of embolism or thrombosis in the lungs are determined by the location, degree and rapidity of the obstruction to pulmonary circulation and by the presence or absence of an associated circulatory incompetency or infection.

It is usually impossible to distinguish between embolic and thrombotic infarcts. Detailed gross dissections and a large series of microscopic sections are needed in order to make an accurate differentiation.

Emboli, oftener than primary thrombi, are believed to be responsible for pulmonary infarctions in children. The emboli come oftener from the iliac and femoral veins than from other peripheral veins.

The fact that the formation of thrombi in a patent ductus arteriosus may be the source of fatal pulmonary embolism constitutes an additional reason for early ligation of a patent ductus arteriosus.

Electrocardiographic studies have not been made in a sufficient number of cases of pulmonary infarction in children to permit appraisal of their diagnostic value.

Roentgenograms of the chest in cases with clinical signs suggesting pulmonary infarction may be helpful in establishing the diagnosis.

That in the majority of cases pulmonary infarction among children is associated with severe infections is verified by the reports in the literature, as well as by the observations in the present series of cases.

The exact mechanism of death due to occlusion of the pulmonary circulation is still a subject of controversy. The general opinion is that the mechanical factor is the initial one, followed by reflex pulmonary atelectasis, bronchial spasm and reflex spasm of several or all of the pulmonary arteries.

Sudden death, with its characteristic picture in cases of pulmonary embolism, occurs more rarely in children than in adults.

The clinical diagnosis of pulmonary infarction is seldom made in children because coexisting disease may mask the symptoms and signs.

VITAMIN C IN THE BLOOD AND URINE OF THE NEWBORN AND IN THE CORD AND MATERNAL BLOOD

BRENTON M. HAMIL, M.D.

BERTHA MUNKS, B.S.

ELSIE Z. MOYER, M.S.

MILDRED KAUCHER, M.S.

AND

HAROLD H. WILLIAMS, Ph.D.*

DETROIT

HERETOFORE, interest in the vitamin C levels in the plasma of the mother, fetus and newborn infant has centered about the function of vitamin C in embryonic and fetal development, the function of the placenta in controlling the supply of the vitamin during gestation and the vitamin C requirements of the newborn infant and of the mother during pregnancy and lactation. Any phase of vitamin C metabolism is complicated by the uncertainty concerning the relative activity in the human body of reduced ascorbic acid and its oxidized form, dehydroascorbic acid. The instability of ascorbic acid also has hindered both the development of accurate methods of quantitative determination and the establishment of the precise requirement for the vitamin by persons of all ages and under various conditions.

Needham,[1] in discussing the relation of ascorbic acid to morphogenetic mechanisms, referred to the ability of the avian and amphibian

*Dr. Williams is now Professor, Department of Biochemistry, Cornell University, Ithaca, N. Y.

From the Department of Pediatrics, Henry Ford Hospital (Dr. Hamil) and the Research Laboratory, Children's Fund of Michigan (Miss Munks, Miss Moyer, Miss Kaucher and Dr. Williams).

The term "vitamin C" has been applied to results obtained in this laboratory by methods which determine greater vitamin C activity than would be found by using methods which determine only ascorbic acid.

The investigation represented in part by this paper was partially supported by a grant from the Nutrition Foundation, Inc., and was made possible by the cooperation of Joseph A. Johnston, M.D., Chief, and members of the Department of Pediatrics, and of J. P. Pratt, M. D., Chief, and members of the Department of Obstetrics, Henry Ford Hospital.

1. Needham, J.: Biochemistry and Morphogenesis, New York, The Macmillan Company, 1942.

embryos to synthesize ascorbic acid and stated that some mammals also possess this ability in fetal life but lose it after birth. He also referred to the work of Biskind and Glick,[2] who pointed to the high content of vitamin C in the corpus luteum and, because it paralleled the progesterone content, assumed that the vitamin may be necessary to the production of the hormone. Ley [3] found that the values for vitamin C in the corpora lutea of 5 nonpregnant women ranged from 24.8 to 48.3 mg. per hundred grams, while for those of 5 women in the second to fifth months of pregnancy the values were from 42.3 to 148.7 mg. per hundred grams. This indicated a definite rise in the vitamin C content as the activity of the organ increased.

Average values for the vitamin C content of the placenta have been reported,[4] ranging from 4.9 to 39.1 mg. per hundred grams. Various authors [5] have shown the vitamin C content of the placenta to be distributed in different amounts among the syncytium, the decidua and the stroma cells. The most active metabolism of vitamin C occurs in the cells of the placental villi.[6] Tonutti and Plate [7] pointed out that the loading of the Golgi apparatus with vitamin C, such as is found in the placenta, is characteristic of an organ through which the vitamin is "passing," in contrast to an organ in which it is "stored." The amount of vitamin C in the placenta is greater in the early months of pregnancy,[5a, b] and Giroud, Ratsimamanga, Rabinowicz, Santos-Ruiz

2. Biskind, G. R., and Glick, D.: Studies in Histochemistry: V. The Vitamin C Concentration of the Corpus Luteum with Reference to Stage of the Estrous Cycle and Pregnancy, J. Biol. Chem. **113**:27-34 (Feb.) 1936.

3. Ley, L.: Ovar und Vitamin C, Arch. f. Gynäk. **164**:408-415, 1937.

4. (*a*) Möller-Christensen, E., and Thorup, C.: Ueber das Vorkommen von Vitamin C in Placenta, Nabelstrangblut, Venenblut und Colostrum, Zentralbl. f. Gynäk. **64**:1858-1861 (Nov. 2) 1940. (*b*) Neuweiler, W.: Ueber den Gehalt der Plazenta an Vitamin C, Schweiz. med. Wchnschr. **65**:539-540 (June 8) 1935. (*c*) Caffier, P., and Ammon, R.: Vergleichende C-Vitamin-Bestimmungen in verschiedenen Placenten, Zentralbl. f. Gynäk. **60**:1-7 (Jan. 4) 1936. (*d*) Neuweiler, W.: Ueber die Vitamin C-Resorption aus der Placenta, Klin. Wchnschr. **17**:1650-1651 (Nov. 19) 1938. (*e*) Muller, J.: Der Vitamin C-Austausch zwischen Mutter und Fetus, ibid. **18**:299-301 (March 4) 1939. (*f*) Hosemann, H., and Athanassiu, G.: Kann eine C-Hypovitaminose die Ursache habituellen Abortierens sein? Zentralbl. f. Gynäk. **63**:1838-1844, 1939.

5. (*a*) Neuweiler, W.: Vitamin C und Placenta, Arch. f. Gynäk. **162**:384-396, 1936; (*b*) Über das Vorkommen von Vitamin C in der Plazenta, Ztschr. f. Geburtsh. u. Gynäak **118**:27-38, 1938. (*c*) Möller-Christensen and Thorup.[4a]

6. Scipiades, E., Jr.: Beiträge zur Frage des Vitamin-C-Gehaltes des menschlichen Mutterkuchens bei intrauterinem Absterben der Frucht, Ztschr. f. Geburtsh. u. Gynäk. **121**:96-113 (June) 1940.

7. Tonutti, E., and Plate, E.: Ueber das Vitamin C in der menschlichen Placenta, Arch. f. Gynäk. **164**:385-397, 1937.

and Cesa [8] reported that the younger the fetus the higher is the ascorbic acid content of its tissues. They assumed that the early fetus has the capacity to synthesize the vitamin. Ingalls,[9] with the indophenol titration method, found that the ascorbic acid content of tissues of infants at birth averaged 38.5 mg. per hundred grams of tissue; from birth to 1 month of age, 28.2 mg., and from 1 to 4 months of age, 10.8 mg. per hundred grams, showing a continuing decrease in tissue storage after birth.

Sweany, Clancy, Radford and Hunter [10] reported values for vitamin C in the tissues of 32 patients who were the subjects of continuous saturation studies for more than a year and who died of various diseases; they gave a rough value of 5 mg. of vitamin C per hundred grams of total body tissue in complete saturation. Much lower values have been reported for a normal child who died at the age of 20 months and for 2 children whose deaths were caused by scurvy.[11] Yavorsky, Almaden and King [12] observed the highest concentrations of vitamin C in the tissues of infants in the age group of 1 to 30 days.

Investigators have recorded values for vitamin C in placental tissue, cord blood serum and infants' and mothers' blood post partum (table 1).

In 1933 Harris and Ray [14] discussed the urinary excretion of vitamin C, and in 1934 Hess and Benjamin showed [15] that infants with manifest scurvy or those with histories of lack of vitamin C in the diet excrete less of the vitamin in the urine than do well nourished infants of the same age. Many data on the urinary excretion of vitamin C have accumulated since that time. The average values for excretion

8. Giroud, A.; Ratsimamanga, R.; Rabinowicz, M.; Santos-Ruiz, A., and Cesa, I.: Capacité de synthèse de l'acide ascorbique chez le fœtus humain, Compt. rend. Soc. de biol. **123**:1038-1040, 1936.

9. Ingalls, T. H.: Ascorbic Acid Requirements in Early Infancy, New England J. Med. **218**:872-875 (May 26) 1938.

10. Sweany, H. C.; Clancy, C. L.; Radford, M. H., and Hunter, V.: The Body Economy of Vitamin C in Health and Disease with Special Studies in Tuberculosis, J. A. M. A. **116**:469-474 (Feb. 8) 1941.

11. Hamil, B. M.; Reynolds, L.; Poole, M. W., and Macy, I. G.: Minimal Vitamin C Requirements of Artifically Fed Infants: A Study of Four Hundred and Twenty-Seven Children Under a Controlled Dietary Regimen, Am. J. Dis. Child. **56**:561-583 (Sept.) 1938.

12. Yavorsky, M.; Almaden, P., and King, C. G.: The Vitamin C Content of Human Tissues, J. Biol. Chem. **106**:525-529 (Sept.) 1934. King, C. G.: The Water-Soluble Vitamins, in: Luck, J. M.: Annual Review of Biochemistry **8**:371-414, 1939.

13. Footnote deleted.

14. Harris, L. J., and Ray, S. N.: The Excretion of Vitamin C in Human Urine and Its Dependence on the Dietary Intake, Biochem. J. **27**:2011-2015, 1933.

15. Hess, A. F., and Benjamin, H. R.: Urinary Excretion of Vitamin C, Proc. Soc. Exper. Biol. & Med. **31**:855-860 (April) 1934.

TABLE 1.—*Values from the Literature for Vitamin C Concentrations in Cord, Maternal and Infant Blood*

Source	Cord Blood Serum			Maternal Blood Serum				Infant Blood Serum				Comment
	No. Samples	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	No. Samples	Obtained at	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	No. Samples	Age, Days	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	
Neuweiler [44]	12	0.4-1.3	0.9	..	.....	.....	...	..	..	.....	...	Arterial; diet apparently adequate
	31	0.5-1.6	1.0	31	Labor	0.4-1.3	0.7	..	..	.....	...	Venous; diet apparently adequate
Möller-Christensen and Thorup [42]	10	0.3-1.4	1.1	10	After birth	0.0-0.8	0.4	..	..	.....	...	
Braestrup [28]	23	0.4-2.6	1.1	22	Delivery	0.1-0.7	0.3	11	1	0.3-0.6	0.4	Infants apparently breast fed;
								12	5	0.1-0.6	0.2	mothers' diets adequate except low
								23	10	0.1-0.5	0.3	intake of citrus fruits by some
Teel and others [23]	9	1.4-2.4	1.8	9	Delivery	0.6-1.0	0.9	..	..	.....	...	Normal diet
	8	0.5-1.8	1.2	8	Delivery	0.1-0.6	0.4	..	..	.....	...	Suboptimal diet
	7	0.5-1.2	0.9	7	Delivery	0.1-0.5	0.2	..	..	.....	...	Deficient diet
Manahan and Eastman [27]	25	0.7-1.7	1.2	25	Delivery	0.2-0.6	0.4	..	..	.....	...	Negro; self-chosen diets
	25	0.8-1.8	1.3	25	Delivery	0.2-1.0	0.5	..	..	.....	...	White; self-chosen diets
	10	1.8-3.5	2.7	10	Delivery	1.0-1.6	1.2	..	..	.....	...	Orange juice given prenatally
Lund and Kimble [25]	94	.....	1.3	94	Delivery	.....	0.7	..	..	.....	...	Adequate diet
McDevitt and others [26]	7	0.3-2.2	1.2	7	Delivery	0.6-1.8	0.0	..	..	.....	...	Two received ascorbic acid prenatally
Mindlin [29]	..	.....	...	30	Day 1	0.1-1.0	0.4	30	0-1	0.5-2.3	1.2	Diet apparently adequate
								15	0	0.8-2.0	1.2	Breast and artificially fed
								5	2	0.4-1.2	0.7	Breast and artificially fed
								10	3	0.4-1.0	0.7	Breast and artificially fed
								5	14	1.1-1.5	1.4	Breast fed, mother receiving 600 mg. of ascorbic acid per day
								3	14	1.3-1.4	1.3	Breast fed, mother receiving 300 mg. of ascorbic acid per day
Ingalls and others [24]	..	.....	...	17	Day 1	0.1-0.7	0.3	..	..	.....	...	Usual hospital diet
				17	Day 7	0.2-0.4	0.3	..	..	.....	...	Usual hospital diet
				9	Day 14	0.2-0.4	0.3	6	13, 14	0.6-1.1	0.9	Usual hospital diet, infants breast fed
				19	Day 1	0.2-1.0	0.4	..	..	.....	...	Usual hospital diet plus 300 or
				19	Day 7	0.8-1.9	1.4	..	..	.....	...	600 mg. asorbic acid; infants
				8	Day 14	1.2-1.6	1.4	5	13, 14	1.1-1.6	1.4	breast fed
Neuweiler, W.: Klin. Wehnschr. 14: 1040-1041, 1935	10	0.7-2.1	1.4	..	.....	.....	...	..	..	.....	...	Arterial
	10	1.9-3.6	2.5	..	.....	.....	...	..	..	.....	...	Venous
Wahren, H., and Rundqvist, O.: Klin. Wehnschr. 16: 1498-1499, 1937	17	0.1-0.5	0.4	17	Delivery	0.0-0.3	0.2	..	..	.....	...	
Elmby, A., and Becker-Christensen, P.: Klin. Wehnschr. 17: 1432-1434, 1938	74	0.2-1.2	...	74	Delivery	0.0-0.0	0.0	..	..	.....	...	Poor diet
	66	0.4-1.9	...	66	Delivery	0.1-0.3	0.2	..	..	.....	...	Fair diet
	44	0.9-3.6	...	40	Delivery	0.2-0.4	0.4	..	..	.....	...	Adequate diet
Concepción, I., and Camara, S.: J. Philippine Islands M. A. 19: 139-143, 1939	30	.....	1.5	30	.....	.....	0.9	..	..	.....	...	
Snelling, C. E., and Jackson, S. H.: J. Pediat. 14: 447-451, 1939	9	0.1-1.5	0.8	9	Delivery	0.0-0.9	0.2	..	..	.....	...	

by healthy infants range from 1 to 3 mg. in twenty-four hours. However, we have found no data on the urinary excretion of vitamin C from the time of birth through the first week of life. If such excretion values indicate the vitamin C nutrition of the infants, then they would provide a means of estimating the amount of the vitamin in fetal, infant and maternal plasma.

Coincident with comprehensive studies of the composition of human milk and of the metabolism of women during the reproductive cycle,[16] the amount of ascorbic acid was determined in venous blood taken from the cut end of the umbilical cord immediately after delivery, in samples of venous blood from the mothers and in capillary blood from the heels of their infants during the first seven days post partum and vitamin C was determined in the urine of the infants during the same period. The infants' urinary excretions of thiamine, riboflavin, nicotinic acid, N^1-methylnicotinamide chloride, pantothenic acid and biotin have been discussed.[17]

PROCEDURE

The subjects of the study were white and Negro male infants whose mothers' economic status was consistent with the private clinic fees of the hospital. The mothers had been in good health before and during uncomplicated pregnancies, terminating in normal deliveries. The infants were born in March, April and May and were breast fed, being weighed before and after each nursing to determine their milk intakes. Details of the care given the infants and of the procedure followed in collection of the urine were presented in a preceding paper.[17] The vitamin C content of the urine (reduced ascorbic acid, dehydroascorbic acid and diketoglucuronic acid) was determined by the method of Roe and Kuether.[18]

The cord blood was obtained at delivery by "stripping" the blood from the cut end of the umbilical cord. The blood sample was placed in the refrigerator and analyzed within twenty-four hours. (Earlier workers[19] have shown that there is no

16. Macy, I. G.; Williams, H. H.; Pratt, J. P., and Hamil, B. M.: Human Milk Studies: XIX. Implications of Breast Feeding and Their Investigation, Am. J. Dis. Child. **70**:135-141 (Sept.) 1945.

17. Hamil, B. M.; Coryell, M.; Roderuck, C.; Kaucher, M.; Moyer, E. Z.; Harris, M. E., and Williams, H. H.: Thiamine, Riboflavin, Nicotinic Acid, Pantothenic Acid and Biotin in the Urine of Newborn Infants, Am. J. Dis. Child., this issue, p. 434.

18. Roe, J. H., and Kuether, C. A.: The Determination of Ascorbic Acid in Whole Blood and Urine Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, J. Biol. Chem. **147**:399-407 (Feb.) 1943.

19. (*a*) Borsook, H. D.; Davenport, H. W.; Jeffreys, C. E. P., and Warner, R. S.: The Oxidation of Ascorbic Acid and Its Reduction in Vitro and in Vivo, J. Biol. Chem. **117**:237-279 (Jan.) 1937. (*b*) Golden, W. R. C., and Garfinkel, L.: Medical Evaluations of Nutritional Status: XII. The Stability of Ascorbic Acid in Whole Blood, Plasma, and Plasma Filtrates, ibid. **144**:447-452 (July) 1942. (*c*) Kassan, R. J., and Roe, J. H.: The Preservation of Ascorbic Acid in Drawn Samples of Blood, ibid. **133**:579-584 (April) 1940. (*d*) Cushman, M., and Butler, A. M.: Use of Cyanide in the Determination of Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **39**:534-539 (Dec.) 1938. (*e*) Kellie, A. E., and Zilva, S. S.: The Catalytic Oxidation of Ascorbic Acid, Biochem. J. **29**:1028-1035, 1935.

TABLE 2.—*Comparison of the Vitamin C Concentrations in Blood and Urine* *

Case		Cord Blood †	Post Partum: 1 Day Blood	1 Day Urine	2 Days Blood	2 Days Urine	3 Days Blood	3 Days Urine	4 Days Blood	4 Days Urine	5 Days Blood	5 Days Urine	6 Days Blood	6 Days Urine	7 Days Blood	7 Days Urine
1	Infant	0.74	0.60	1.2	....	1.1	....	0.9	0.32	0.9	....	....	....	....	....	...
	Mother		0.06	....	....	....	....	....	0.06	....	....	....	....	....	....	...
2	Infant	2.02	1.29	....	....	28.7	....	13.3	0.32	10.2	....	....	....	....	....	...
	Mother		0.73	....	....	....	....	....	0.54	....	....	....	....	....	....	...
3	Infant	2.18	....	10.8	....	23.4	....	12.7	0.99	....	....	....	....	....	....	...
	Mother		0.40	....	....	....	....	....	0.75	....	....	....	....	....	....	...
4	Infant	0.71	0.66	1.1	....	0.8	....	0.8	....	0.6	....	0.6	....	....	....	...
	Mother		0.04	....	....	....	....	....	....	....	....	....	....	....	....	...
5	Infant	....	....	....	0.86	10.9	....	....	....	....	....	....	0.67	23.6	....	...
	Mother		....	....	0.24	....	....	....	....	....	....	....	0.67	....	....	...
6	Infant	....	....	25.5	....	....	0.81	....	....	2.9	....	....	....	2.0	0.91	2.2
	Mother		....	....	....	....	....	....	0.28	....	....	....	....	....	0.34	...
7	Infant	2.11	0.26	21.9	....	....	....	12.9	....	....	0.70	1.1	....	....	....	...
	Mother		....	....	0.82	....	....	....	....	....	0.60	....	....	....	....	...
8	Infant	1.96	0.85	....	....	....	....	....	....	....	....	....	....	....	....	...
	Mother		0.83	....	....	....	....	....	....	....	....	....	....	....	....	...
9	Infant	1.08	0.70	....	0.70	7.4	....	5.9	....	....	0.59	1.0	....	....	....	...
	Mother		0.40	....	0.52	....	....	....	....	....	0.40	....	....	....	....	...
10	Infant	1.81	0.20	30.2	....	8.5	....	17.6	....	8.4	0.65	3.6	....	....	....	...
	Mother		....	....	0.42	....	....	....	....	....	0.26	....	....	....	....	...
11	Infant	0.66	0.60	42.4	....	8.1	....	7.1	0.74	....	....	....	....	....	....	...
	Mother		....	....	....	....	....	....	0.51	....	....	....	....	....	....	...
12	Infant	2.06	0.63	....	....	....	....	20.2	....	3.4	0.32	2.7	....	....	....	...
	Mother		1.19	....	....	....	....	....	....	....	0.63	....	....	....	....	...
13	Infant	1.37	....	....	....	4.2	....	....	0.18	3.7	....	....	....	....	....	...
	Mother		0.26	....	....	....	....	....	0.35	....	....	....	....	....	....	...
14	Infant	1.19	0.44	10.9	....	....	....	12.9	....	6.5	....	11.3	0.59	....	....	...
	Mother		0.28	....	....	....	....	....	....	....	....	....	0.20	....	....	...
15	Infant	....	0.59	3.1	....	3.7	....	0.0	0.20	4.8	....	....	....	....	....	...
	Mother		0.79	....	....	....	....	....	0.83	....	....	....	....	....	....	...
16	Infant	1.22	0.44	7.8	....	3.9	....	....	0.63	1.9	....	0.8	....	....	....	1.0
	Mother		0.22	....	....	....	....	....	0.24	....	....	....	....	....	....	...
17	Infant	....	1.24	7.5	....	....	....	2.3	....	6.2	....	....	0.67	....	....	...
	Mother		0.24	....	....	....	....	....	....	....	....	....	0.59	....	....	...
18	Infant	1.81	....	....	....	30.3	....	11.1	0.74	....	....	3.2	....	....	....	4.7
	Mother		....	....	....	....	....	....	0.16	....	....	....	....	....	....	...
19	Infant	....	....	....	....	....	0.93	5.5	....	11.5	....	....	....	4.3	0.48	4.4
	Mother		....	....	....	....	....	....	0.24	....	....	....	....	....	0.28	...
20	Infant	2.18	0.84	22.5	....	22.3	....	8.2	0.99	9.9	....	....	....	....	....	...
	Mother		0.79	....	....	....	....	....	0.79	....	....	....	....	....	....	...
21	Infant	....	....	....	0.88	3.7	....	21.2	....	10.1	0.40	2.7	....	....	....	...
	Mother		....	....	0.77	....	....	....	....	....	0.57	....	....	....	....	...
22	Infant	....	0.24	1.4	....	7.2	....	....	0.22	1.1	....	1.1	....	0.0	0.19	...
	Mother		0.08	....	....	....	....	....	0.08	....	....	....	....	....	0.24	...
23	Infant	....	....	....	0.58	0.8	....	1.8	....	....	....	....	0.16	0.6	....	0.2
	Mother		....	....	0.16	....	....	....	....	....	....	....	0.12	....	....	...
24	Infant	0.95	1.72	....	....	1.5	....	....	....	0.5	0.17	0.5	....	....	....	0.4
	Mother		....	....	0.14	....	....	....	....	....	0.10	....	....	....	....	...

* All values are expressed in milligrams per hundred cubic centimeters.
† Venous.

appreciable loss of ascorbic acid in whole blood stored twenty-four hours in a refrigerator.) Samples of venous blood were obtained from the mothers three to four hours after a breakfast from which foods containing ascorbic acid had been excluded. Capillary blood was obtained from the heel of the infant with a collecting pipet without regard to the time of nursing, since it has been shown that the ascorbic acid in the small amount of milk ingested at one feeding does not produce a rise in the plasma concentration of the vitamin.[20] Samples of blood were analyzed within a few hours after collection by the method of Farmer and Abt.[21]

RESULTS

Table 2 shows values obtained for plasma concentration of reduced ascorbic acid in samples of cord blood, of capillary blood from the infants and of venous blood obtained from the mothers, together with the amounts of vitamin C excreted in the infant's urine. The average value for the cord blood was over twice that noted for the infants' blood within twenty-four hours after delivery. The average value for the babies' blood was a third greater than that for the mothers' blood. However, the changes in concentration during the first week varied widely, some of the infants showing increases and others decreases. The values for the mothers show similar variations in trend during the first week post partum, but the changes are smaller. There was wide variation in the vitamin C concentration of the urine of the infants during each consecutive twenty-four hour period. The range for the first day was from 1.1 to 42.4 mg. per hundred cubic centimeters, but in almost all instances the concentration in the urine of each infant decreased greatly during the first week of life.

Daily intakes of vitamin C were calculated from the volumes of milk ingested and the average concentration of the vitamin in human milk for the respective days post partum.[22] Daily excretions of the vitamin were determined from the ratio of total fluid intake and volume of urine to the concentration of the vitamin (table 2), as described in the previous paper.[17] The 24 infants had an average birth weight of 3,595 Gm. (7 pounds 14.8 ounces) ranging from 2,650 to 4,230 Gm. (5 pounds 6 ounces to 9 pounds 5 ounces). The average on the second day was 3,397 Gm. (7 pounds 7½ ounces), an initial neonatal loss of 198 Gm. (7 ounces). Thereafter, the average daily increase in weight was about 1 ounce (453 Gm.), bringing the average weight on the eighth day to 3,540 Gm. (7 pounds 13 ounces), less than 2 ounces (900 Gm.) below the weight at birth. Although there was no intake of the vitamin,

20. Mindlin, R. L.: The Relation Between Plasma Ascorbic Acid Concentration and Diet in the Newborn Infant, J. Pediat. **13**:309-313 (Sept.) 1938.

21. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146-150 (March) 1936.

22. Munks, B.; Robinson, A.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXV. Ascorbic Acid and Dehydroascorbic Acid in Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:176-181 (Sept.) 1945.

the average amount of vitamin C excreted the first day, 5 mg., approximated the amounts excreted during each of the following six days. The average amounts excreted each day during the first week of life ranged from 4 to 6 mg., while the average intake increased many times during the same period.

COMMENT

In evaluating the plasma levels, the fact must be considered that the intake of vitamin C by the infants depended on the amounts available in the breast milk and increased from zero, on the first day, to an average of 37 mg. on the seventh day. The values for plasma vitamin C in the blood of the umbilical cord and in the samples of maternal and infant blood taken during the neonatal period (table 2) are in harmony with those given in the literature (table 1). The conclusion that has been drawn from the gradual decrease in the serum values for some infants and mothers during this period seems to be a logical one: that the increased fetal demand for the vitamin is met at the expense of the mother if need be, and that the same circumstance applies to the requirements for lactation in the postpartum period. However, the data given in table 2 indicate that other factors are involved and that individual variations are too great to justify an interpretation based on averages alone.

Teel, Burke and Draper [23] observed that the amount of ascorbic acid in the plasma of adequately nourished women tended to decrease as pregnancy advanced even though the dietary ascorbic acid was increased. At delivery the amount of the vitamin in the plasma of the cord blood was much greater than that in the maternal plasma. Blood from the umbilical vein contained slightly more ascorbic acid than that from the umbilical artery. They concluded that as long as appreciable amounts of ascorbic acid are present in the maternal serum, the fetus will take what it needs. Ingalls, Draper and Teel [24] showed that after birth the breast-fed infant may obtain an adequate supply of vitamin C even though low plasma ascorbic acid concentration indicates that the mother's diet is relatively deficient. They concluded that the increased maternal need for the vitamin during pregnancy extends into the nursing period as well.

Lund and Kimble,[25] on the other hand, did not find that the vitamin C requirement of the mother increased during pregnancy. Although

23. Teel, H. M.; Burke, B. S., and Draper, R.: Vitamin C in Human Pregnancy and Lactation: I. Studies During Pregnancy, Am. J. Dis. Child. **56**: 1004-1010 (Nov.) 1938.

24. Ingalls, T. H.; Draper, R., and Teel, H. M.: Vitamin C in Human Pregnancy and Lactation: II. Studies During Lactation, Am. J. Dis. Child. **56**: 1011-1019 (Nov.) 1938.

25. Lund, C. J., and Kimble, M. S.: Some Determinants of Maternal and Plasma Vitamin C Levels, Am. J. Obst. & Gynec. **46**:635-647 (Nov.) 1943.

there was a slight tendency to lowered plasma levels twenty-four hours after delivery in half the cases, they did not consider this to be significant of a greater demand on the mother's vitamin C stores incident to labor. Study of individual pairs of mothers and infants showed that if the maternal plasma level was very low that of the infant might be from five to eight times as great; when the maternal values were high, the fetal values might be only 50 per cent higher. Administration of ascorbic acid to the mother parenterally caused an elevation of values for both maternal and fetal plasma to equal levels. Rapid reduction of the maternal level to normal followed this period, while the fetal values remained high. The authors concluded that the placenta acts as a barrier to reentrance of ascorbic acid to the maternal circulation, and they expressed the belief that this mechanism of "selective retention" would account for the difference between maternal and fetal values throughout all ranges, as well as for the dependence of the fetus on the mother for the vitamin. McDevitt, Dove, Dove and Wright [26] and Manahan and Eastman,[27] because of the relatively high concentrations in fetal blood (two to four times that of maternal blood), suggested that the placenta exerted a "selective action" with respect to the vitamin.

Braestrup [28] calculated averages for mothers' blood at delivery of 0.26 mg., for cord blood, of 1.07 mg., and for infants' blood at birth, of 0.69 mg., per hundred cubic centimeters. The concentration of the vitamin in the infants' plasma decreased about 50 per cent in the first twenty-four hours and at 10 days of age was practically at the level of the mothers' serum. He suggested that in order to bring these data into agreement with the hypothesis that vitamin C is concentrated in the placenta, it must be assumed that there is a considerable loss of the vitamin in the fetus. Mindlin's [29] values are essentially in agreement with those of Braestrup, and the data presented by Fleming and Sanford,[30] when interpreted in the light of the other values in the literature, also are in agreement.

In table 3 the estimated average daily excretion of vitamin C is given, together with the calculated amount of the vitamin in the

26. McDevitt, E.; Dove, M. A.; Dove, R. F., and Wright, I. S.: Selective Filtration of Vitamin C by the Placenta, Proc. Soc. Exper. Biol. & Med. **51**:289-290 (Nov.) 1942.

27. Manahan, C. P., and Eastman, N. J.: The Cevitamic Acid Content of Fetal Blood, Bull. Johns Hopkins Hosp. **62**:478-481 (May) 1938.

28. Braestrup, P. W.: The Content of Reduced Ascorbic Acid in Blood Plasma in Infants, Especially at Birth and in the First Days of Life, J. Nutrition **16**:363-373 (Oct.) 1938.

29. Mindlin, R. L.: Variations in the Concentration of Ascorbic Acid in the Plasma of the Newborn Infant, J. Pediat. **16**:275-284 (March) 1940.

30. Fleming, A. W., and Sanford, H. N.: Vitamin C Content of the Blood in Newborn Infants, J. Pediat. **13**:314-321 (Sept.) 1938.

extracellular water (determined as the plasma value, multiplied by 25 per cent of the body weight [31]). The vitamin C excretion was 0.0 to 16.2 mg. per day during the first week, while the amount of vitamin C in the circulating body fluids ranged from 1.1 to 13.1 mg. per day. From the figures it is evident that in many instances the daily urinary excretion of ascorbic acid was as great as the total amount of the vitamin in the infant's circulating fluid. Mindlin [20] demonstrated that the high concentration of ascorbic acid in the blood at birth falls rapidly during the period of ascorbic acid starvation. The reason for this decrease is readily understood when the amount excreted in the urine is considered in relation to the level of the vitamin in the blood, particularly at a time when the infant is not yet receiving appreciable amounts of the vitamin in the breast milk.

Flexner, Wilde, Proctor, Cowie, Vosburgh and Hellman,[31a] using the tracer technic, found that the extracellular water content of newborn infants, expressed as in percentage of body weight is 1.7 times that of the adult. They presented

TABLE 3.—*Vitamin C in Circulating Fluid and Daily Urine Excretion*

Interval Post Partum, Days	Number of Samples	Circulating Fluid,* Mg./Day	Ascorbic Acid in Urinary Excretion, Mg./Day
1	10	5.4	5.2
2	4	6.5	3.1
3	1	8.3	5.4
4	5	3.8	5.4
5	7	3.9	3.5
6	1	1.5	1.5
7	2	6.9	10.0

* Plasma volume multiplied by one-fourth the body weight.

evidence from the literature that the processes of growth throughout gestation and postnatal life are accompanied with an increase in the ratio of the intracellular and the extracellular body water. McCance [31b] summarized the function of the infant's kidney in contrast to that of adults: Following ingestion of large quantities of water both young animals and young humans excrete the water at much slower rates than do corresponding adults. The osmotic pressure of the urine in infancy is low and only rises to adult levels when the serum becomes highly abnormal. . . . The glomerular filtration rates in infancy appear to vary with the hydration of the body, whereas in adults these are relatively constant. . . . There is good evidence

31. Darrow, D. C.: Congenital Alkalosis with Diarrhea, J. Pediat. **26**:519-532 (June) 1945. Harrison, H. E.; Darrow, D. C., and Yannet, H.: The Total Electrolyte Content of Animals and Its Probable Relation to the Distribution of Body Water, J. Biol. Chem. **113**:515-529 (March) 1936.

31a. Flexner, L. B.; Wilde, W. E.; Proctor, N. K.; Cowie, D. B.; Vosburgh, G. J., and Hellman, L. M.: The Estimation of Extracellular and Total Body Water in the Newborn Human Infant with Radioactive Sodium and Deuterium Oxide, J. Pediatrics **30**:413-415 (April) 1947.

31b. McCance, R. A.: The Physiology of the Kidney in Infancy and Its Importance in Pediatrics, Schweiz. med. Wchnschr. **76**:857-860 (Sept. 16-21) 1946; abstracted, Quart. Rev. Pediat. **2**:298-299 (May) 1947.

that certain tubular functions are defective for some time after birth. Reabsorption of urea, which is probably a passive process, seems to take place to about the same extent in infants as in adults, but the excretion of urea has recently been found to be very low in babies a few days old. There are suggestions in the literature that the formation and excretion of ammonia (as judged by adult standards) may be defective in the early weeks of life. Differences in cellular metabolism no doubt underlie all these differences in function.

The highest concentration (table 2), 42.4 mg. vitamin C per hundred cubic centimeters, was excreted nineteen hours after birth by an infant whose cord blood serum contained 0.66 mg. and whose venous blood serum showed 0.60 mg. of vitamin C per hundred cubic centimeters about five hours after birth. One infant (table 2, case 17) during his first twenty-four hours excreted 64 cc. of urine, containing 6.1 mg. of vitamin C. This was enough to have lowered the vitamin C level of each one hundred cubic centimeters of circulating fluid over 0.6 mg. However, the blood obtained from this infant at the twenty-fourth hour of life contained 1.24 mg. of vitamin C per hundred cubic centimeters of serum. Another infant (case 20) voided urine eleven hours after delivery which contained 4.4 mg. of vitamin C. At twenty-two hours of age the blood serum contained 0.84 mg. per hundred cubic centimeters; one hour later the infant voided 8.2 mg. of vitamin C. The total excretion, 12.7 mg., could have lowered the vitamin C of his circulating fluid 1.4 mg. per hundred grams during the first twenty-four hours of life. A third infant (case 7), whose cord blood showed 2.1 mg. per hundred cubic centimeters, had a blood serum content of 0.26 mg. per hundred cubic centimeters. Eighteen hours after birth 7.9 mg. of vitamin C was excreted in the urine, which could cause a decrease of 0.8 mg. of vitamin C per hundred grams of circulating fluid. The blood value on the fifth day of life showed 0.70 mg. per hundred cubic centimeters of serum.

Mindlin [20] stated that even though the ascorbic acid of the blood of the newborn falls to a low level it can be raised to normal by an adequate intake of breast milk rich in the vitamin. Since newborn infants have high concentrations of vitamin C in the blood at birth (tables 1 and 2), it is not surprising that the concentrations in the urine are also high. Harris and Ray [14] and Hess and Benjamin [15] showed that after large vitamin C intakes both adults and children had continued losses of vitamin C, even after the intakes had been reduced. Similarly, the well nourished newborn infant excretes appreciable amounts of vitamin C during the first few days of life, when he is receiving little or none from breast milk. If the infant is not supplied with vitamin C, the blood level decreases and there is absolute disappearance of the vitamin from the urine.[32]

32. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10**:577-591 (May) 1937.

We have found no data on the urinary excretion of ascorbic acid by normal infants during the first week of life. Neuweiler [33] reported for the excretion of the vitamin by 45 infants on the ninth day of life values ranging from 0.9 to 19.5 mg., with an average of 5.2 mg. per day, an amount approximating the average of 6.3 mg. per day estimated for the infants in the present study on their seventh day of life. Other authors have reported the results of similar studies made on older infants.[34] Several investigators have stated that the healthy infant excretes from 1 to 3 mg. of ascorbic acid in twenty-four hours. Denoyelle and Sirand [34a,b] observed that the ingestion of as little as 5 mg. of ascorbic acid by properly nourished infants 3 to 10 months of age resulted in a slight, but definite, rise in the ascorbic acid excretion of the urine within one to three hours. The concentrations varied from 0.1 to 1.3 mg. per hundred cubic centimeters, they varied from one time to another during the day and varied for each infant. The curve of the concentrations did not appear to be directly influenced by the hour of feeding, nor did the rhythm of elimination follow a regular pattern, even for infants who received identical food. Diuresis influenced the concentration by dilution, the concentration of ascorbic acid at each voiding being influenced by the volume of urine. Laurin,[35] in ascorbic acid saturation tests judged by urinary excretion, showed that healthy breast-fed infants between 4 weeks and 5 months of age showed saturation on the first or second day. Slobody, Benson and Mestern [36] tested 77 mothers and their newborn infants by intradermal injection of a dye and found that "the intradermal test for vitamin C indicates the same maternal–newborn infant relationship as the plasma ascorbic acid levels. The infant tends toward saturation regardless of the mother's tissue concentration." They also stated: "The intradermal tests in the infant on subsequent days for a week or more after birth remained approximately the same. The high vitamin C levels are thus not temporary phenomena after birth, but remain constant."

---

33. Neuweiler, W.: Vitamin C-Stoffwechsel bei Neugeborenen, Ztschr. f. Vitaminforsch. **6**:75-82 (Jan.) 1937.

34. (*a*) Denoyelle, L., and Sirand, E.: Elimination urinaire de l'acide ascorbique chez le nourrisson sain, Compt. rend. Soc. de biol. **129**:655-657, 1938; (*b*) Influence du régime alimentaire sur l'élimination urinaire de l'acide ascorbique chez le nourrisson sain, ibid. **129**:756-758, 1938, (*c*) Harris, L. J., and Ray, S. N.: Diagnosis of the Vitamin-C Substitution by Urine Analysis with a Note on the Antiscorbutic Value of Human Milk, Lancet **1**:71-77 (Jan. 12) 1935.

35. Laurin, I.: Some Ascorbic Acid Saturation Tests on Infants, Acta Paediat. **20**:352-369, 1938.

36. Slobody, L. B.; Benson, R. A., and Mestern, J.: A Comparison of the Vitamin C in Mothers and Their Newborn Infants, J. Pediat. **29**:41-44 (July) 1946.

Infants 4 days old were studied by Ley.[37] The amounts of vitamin C excreted by 2 healthy babies, 0.6 and 0.7 mg. per day, correspond to the lowest value in table 2. Two infants in poor nutritional states who were receiving both breast milk and cow's milk excreted 0.3 and 0.2 mg. during the fourth day. Two other infants, given 50 mg. of ascorbic acid per day in addition to milk, excreted 7.5 and 10 mg. during the tenth and twelfth days. Low daily excretion values were observed by Hahn,[38] beginning with 0.4 mg. per day at the second week of life and increasing during the first year of life but never exceeding 1.2 mg. per day. Denoyelle and Sirand[34a] reported values of 1 to 3 mg. of vitamin C per day for infants 3 to 10 months of age. Harris and Ray[34c] also reported low excretions (1.1 to 1.8 mg. per day) for infants 17 weeks to 13 months old.

As early as 1934 Szent-Györgi[39] suggested that the infant's requirement for vitamin C is not far from 25 mg. per day. By test doses on 17 infants during the second week of life, Neuweiler[33] arrived at the conclusion that sucklings require 6 mg. of vitamin C per kilogram of body weight per day. In the present study, the average weight of the infants during the first week of life was 34,500 Gm. (7 pounds, 3 ounces). Estimated on the basis of the 6 mg. suggested by Neuweiler, the requirement for vitamin C is 21 mg. per day. This value is close to the calculated value of 16 mg. of vitamin C per day unaccounted for during the first week of life, when the infants' intakes were estimated to average 21 mg. per day and their excretions 5.0 mg. per day.

The high concentration of vitamin C in the first urine passed after birth and the subsequent lowering of the plasma concentration at once suggest that the physiologic processes of intrauterine life require greater tissue saturation of vitamin C than is necessary in the gaseous environment of extrauterine existence. This is emphasized by the fact that excretion continues although in general the plasma concentration falls slowly during the early neonatal period, when little or no vitamin C is being consumed by the infant.

It has been shown that the concentration of vitamin C in fetal tissues decreases[8] with age, and therefore with the decreasing rate of growth and the increased formation of fetal hemoglobin to compensate for the decrease in oxygen saturation which accompanies the latter part of pregnancy.[40] There is a continual decrease in the concentration of

37. Ley, L.: Die Bedeutung des Vitamin C für das Neugeborene, Klin. Wchnschr. **16**:1425-1428 (Oct. 9) 1937.

38. Hahn, U.: Besitzt der junge Säugling eine Sonderstellung im C-Vitamin-Stoffwechsel? Ztschr. f. Kinderh. **57**:442-445, 1935.

39. Szent-Györgi, A.: Die medizinsche Bedeutung des Vitamins C, Deutsche med. Wchnschr. **60**:556-557 (April 13) 1934.

40. Barcroft, J.: The Oxygen Capacity of Foetal and Neo-Natal Blood, Schweiz. med. Wchnschr. **71**:246-247 (March 15) 1941.

vitamin C in the tissues of the infant after birth.[9] If this vitamin has a function in cell chemistry (oxidation-reduction),[41] these facts would be in harmony. More of the vitamin would be required for the state of low oxygen tension of the blood in intrauterine life than would be needed after birth when there is a free exchange through the lung. The amount in the tissues above the level needed for optimum tissue function in extrauterine life would be excreted. Such a theory would obviate the necessity of placing any "selective" or "barrier" function on the placenta, in that the fetal tissues would hold what was needed for this physiologic function as a result of other factors accompanying the state of pregnancy.

Bowman and Muntwyler[42] observed in doves and rats that ether anesthesia resulted in a short period of increased excretion of ascorbic acid. This finding had been observed by Zilva.[43] When ether was employed as a general anesthetic during intravenous injection of various ascorbic acid compounds into guinea pigs, the amounts excreted in urine per twenty-four hours increased 50 to 100 per cent over those excreted when no anesthetic was used. This excretion did not prevent the fixation of the vitamin in the tissues in direct ratio to the antiscorbutic potency of the material injected. Sayers, Sayers, Liang and Long,[44] in discussing the ascorbic acid content of tissues following hemorrhage, referred to these observations of Bowman and Muntwyler[42] as evidence of increased urinary excretion following stress (ether anesthesia), in explanation of the increased plasma level which they observed in rats following hemorrhage. In these studies either the ether anesthesia or the fatal slow hemorrhage would have produced a state of tissue anoxia, which would have been followed by the mobilization of ascorbic acid in animals such as the rat, which is capable of synthesis of the vitamin were it of value in such a state. In considering the elements of anesthesia or physical stress incident to labor and delivery of the infant as related to excretion of the vitamin by the infant, there seemed to

41. Possible Role of Ascorbic Acid in Animal Tissues, editorial J. A. M. A. **114**:1668 (April 27) 1940.

42. Bowman, D. E., and Muntwyler, E.: Urinary Excretion of Ascorbic Acid in the Dog Following Ether Anesthesia, Proc. Soc. Exper. Biol. & Med. **33**:437-438 (Dec.) 1935; Further Experiments upon the Excretion of Ascorbic Acid in the Urine Following Ether Anesthesia, J. Biol. Chem. **114**:14, 1936.

43. Zilva, S. S.: The Behaviour of *l*-Ascorbic Acid and Chemically Related Compounds in the Animal Body: The Influence of Generalized Ether Anesthesia on Their Urinary Excretion, Biochem. J. **29**:2366-2368, 1935; The Behaviour of *l*-Ascorbic Acid and Chemically Related Compounds in the Animal Body: Antiscorbutic Activity in Relation to Retention by the Organism, ibid. **29**:1612-1616, 1935.

44. Sayers, G.; Sayers, M. A.; Liang, T. Y., and Long, C. N. H.: The Cholesterol and Ascorbic Acid Content of the Adrenal, Liver, Brain, and Plasma Following Hemorrhage, Endocrinology **37**:96-110 (Aug.) 1945.

be no correlation with the length of labor or the type of anesthetic used. The high concentration in the urine continued for several days, whereas the increased excretion by the animals was transient and returned to normal within twenty-four hours.

In support of the thesis that the anoxemic state of fetal life may require more tissue storage of the vitamin is the work of Borsook, Davenport, Jeffreys and Warner,[19a] who attempted to show the difficulty of determining the reversible oxidation-reduction potential of ascorbic acid and to follow, guided by the in vitro findings, the fate of dehydroascorbic acid in vivo. The rates of appearance of all the manifestations of the irreversible changes in dehydroascorbic acid synthesis exhibited the same dependence on hydrogen ion concentration (less than p_H 4 in aqueous solution at ordinary temperature). Ascorbic acid could be made to take up the equivalent of at least three atoms of oxygen in the course of oxidation. Ascorbic acid in whole blood was found to be relatively stable; about three fourths of the amount added was recovered in reduced form after four hours, often as much as 95 to 97 per cent. It was shown, however, that the vitamin is rapidly reduced in the tissues, owing to the presence of glutathione. Barron, DeMeio and Klemperer [45] suggested that by virtue of its high reducing power ascorbic acid seems to be one of the substances which maintains the equilibrium necessary for the harmonious interrelations of cellular oxidation and reduction. They showed that ascorbic acid was not autoxidizable at physiologic hydrogen ion concentrations in acid and neutral solutions. It was, however, autoxidizable in alkaline solutions, the rate of oxidation increasing with the p_H. Of the metallic salts tested, copper was the only catalyst for the oxidation of ascorbic acid, and the maximum rate of oxidation with copper as the catalyst was reached at p_H 6.95. Hemochromogens used for the oxidation of ascorbic acid acted as catalysts at p_H 6.39. In normal human newborn infants the average p_H of blood from the umbilical artery is 7.32, and that of blood of the umbilical vein, 7.35.

Windle [46] stated that the more dilute solutions of hemoglobin from the human fetus took up oxygen less readily than did the hemoglobin of the mother. However, in buffered (p_H 7.4) suspensions, fetal corpuscles, like whole fetal blood, became more highly saturated with oxygen at low partial pressure than did similar suspensions of maternal corpuscles. Barcroft [40] suggested that the anoxemia in the fetus of the

45. Barron, E. S. B.; DeMeio, R. H., and Klemperer, F.: Studies on Biological Oxidations: V. Copper and Hemochromogens as Catalysts for the Oxidation of Ascorbic Acid; the Mechanism of the Oxidation, J. Biol. Chem. **112**:625-640 (Jan.) 1936.

46. Windle, W. F.: Physiology of the Fetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders Company, 1940.

late gestation period might have a direct effect on some tissues, possibly the bone marrow promoting the process of production of hemoglobin. He admitted, however, that to maintain adequate oxygen content the fetus requires much more hemoglobin than is actually saturated with oxygen. Windle [46] explained that the hemoglobin of the fetus differs from that of the mother's blood and that the difference is such that oxygen is taken up with greater ease at the low partial pressures which occur in the placenta. After birth, it is desirable that this relation be reversed. When the blood is oxygenated in the lungs, it finds a greater oxygen tension prevailing there than in the placenta, and the avidity of the fetal hemoglobin is no longer needed. On the other hand, an active tissue metabolism calls for more efficient transfer of oxygen in the other direction, at the peripheral capillaries. He implied that differences in p_H may be influential in accomplishing this. The conditions of fetal respiration fluctuate normally from moment to moment during the last few days of pregnancy, owing to uterine contractions. Although 95 per cent saturation with oxygen may be attained at times, it is doubtful whether the average amount available to the fetus during the latter part of fetal life can be as great as it was earlier; therefore a state of physiologic anoxemia exists. If vitamin C has a chemical function in a reversible oxidation-reduction carrier system,[41] which is dependent on hydrogen ion concentration, there may be many factors in the late gestation period which contribute to abundant urinary excretion of the vitamin after birth.

The capacity of the human fetal bladder varies from 40 to 70 cc. between the seventh month and birth.[46] The urine in the bladder at any time is no index of the excretion, since the amniotic fluid contains an indeterminable quantity of urine. In considering the change in the renal function of the fetus at birth, we quote from Windle: [46]

> Excretion begins early in the true kidney (9 weeks in the human) and is continuous but slow. The mesonephros functions before the true kidney (metanephros) and for some time after the latter has taken over urine production. The fetal glomerulus (capillary tuft and Bowman's capsule) gives rise to a dialysate from the blood and the rapidity with which this forms is related to fetal capillary pressure, osmotic pressure of the fetal blood colloids, carbon dioxide level of the fetal blood and other factors. Some substances may be contributed to the glomerular fluid by secretory activity of the cells of the proximal convoluted tubules. Shortly after elimination begins in the glomerulus and proximal tubule, resorption of water and highly soluble compounds occurs in the proximal tubules and the thin segments of Henle's loop in response to an altered osmotic balance in the blood which has passed through the glomeruli. . . .
>
> Provisions are made for rapidly altering many of the organism's vital activities at the time of birth. Changes are encountered in the circulatory and nervous systems and especially in the respiratory mechanism where a sudden shift from placental to lung breathing takes place. It is therefore not surprising to find dramatic structural and functional changes in the kidneys at the time of birth.

High columnar epithelium invests the fetal renal glomerulus. This, the visceral layer of Bowman's capsule, forms a heavy sac which confines the glomerular tufts. Its comparatively low permeability must serve as an impediment to rapid glomerular elimination. The fetus not only does not need a mechanism for rapid filtration in its kidneys, but such a mechanism might actually be detrimental, for it would seriously disturb the fluid balance in utero. When placental elimination is suddenly abolished at birth the columnar epithelial investments of the renal glomeruli burst, allowing the glomerular vascular loops to expand and to come directly into contact with the capsular space. Henceforth glomerular filtration is greatly enhanced.

Perhaps this purely physiologic change is the only explanation necessary for the high concentrations of vitamin C in the urine of the newborn infant. It seems, however, that the data presented may indicate that the conditions governing the comparatively low permeability of the fetal glomerulus were also operative in the accomplishment of the high saturation of vitamin C of the tissue cells of various, possibly all, organs of the fetal body. The increased excretion at birth is possibly due not only to histologic alteration in the renal glomeruli but also to the changes in capillary pressure, osmotic pressure of blood colloids, carbon dioxide level of the blood and other physical alterations in the circulation which occur incident to the change from an aquatic to a gaseous environment.

SUMMARY

The vitamin C was determined in blood from the umbilical cord, in venous blood of the mothers and in the capillary blood and the urine of the infants during their first week of life.

The vitamin C content of cord blood ranged from 0.66 to 2.18 mg. per hundred cubic centimeters. Maternal serum contained from 0.04 to 1.19 mg. per hundred cubic centimeters on the first day post partum, while values for the infants' blood ranged from 0.20 to 1.72 mg. per hundred cubic centimeters. The changes in the level of vitamin C in the blood varied widely among the individual women and infants during the first week post partum. In general, concentrations of vitamin C in urine were high during the first two days of life but dropped to low levels by the fourth day. The declining levels of vitamin C in the urine and plasma during the first week of life suggest that the physiologic processes of intrauterine life require greater tissue saturation of the vitamin than is necessary in the gaseous environment of extrauterine existence.

660 Frederick Street.

THIAMINE, RIBOFLAVIN, NICOTINIC ACID, PANTOTHENIC ACID AND BIOTIN IN THE URINE OF NEWBORN INFANTS

BRENTON M. HAMIL, M.D.

MARGARET CORYELL, Ph.D.

CHARLOTTE RODERUCK, M.S.

MILDRED KAUCHER, M.S.

ELSIE Z. MOYER, M.S.

MARY ELLEN HARRIS, B.S.

AND

HAROLD H. WILLIAMS, Ph.D.

DETROIT

THE available literature contains only one record of the urinary excretion of the vitamins of the B complex by normal infants during the first week of life. Neuweiler [1] measured the twenty-four hour excretions of thiamine by babies 1 to 10 days old and obtained single values at the ages of 12, 14, 15, 18, 19, 23, 46, 63 and 112 days. He observed that the excretion of thiamine by the nursing child is small, but is somewhat higher during the first four or five days of life than later. He observed also that an oral supplement of thiamine to the baby was well absorbed, for it appeared in the urine immediately. When an injection of 25 mg. of thiamine hydrochloride was given the mother shortly before delivery, the urinary excretion of the infant showed relatively small increases in thiamine concentration, which declined after three days. Neuweiler expressed the opinion that the placenta acts as a barrier, or regulator, preventing the possibility of overloading the fetus with thiamine.

---

* Dr. Williams is now Professor, Department of Biochemistry, Cornell University, Ithaca, N. Y.

From the Department of Pediatrics, Henry Ford Hospital (Dr. Hamil) and the Research Laboratory, Children's Fund of Michigan (Dr. Coryell, Miss Roderuck, Miss Kaucher, Miss Moyer, Miss Harris and Dr. Williams).

The investigation represented in part by this paper was partially supported by a grant from the Nutrition Foundation, Inc., and was made possible by the cooperation of Joseph A. Johnston, M.D., Chief, and members of the Department of Pediatrics, and of J. P. Pratt, M.D., Chief, and members of the Department of Obstetrics, Henry Ford Hospital.

1. Neuweiler, W.: Ueber die B_1-Ausscheidung im Urin bei Neugeborenen, Ztschr. f. Vitaminforsch. **13**:280-286, 1943.

The synthesis of thiamine by intestinal flora [2] has been demonstrated, but the availability of the synthesized vitamin to the organism is debatable.[3] Since thiamine may be destroyed during metabolic processes and is excreted also as the pyrimidine and thiazole fractions of the original molecule, values for thiamine concentration in the urine do not represent the total excretion.

Toverud [4] found that a woman seven to nine months pregnant required four to five times as much thiamine as the nonpregnant woman. Lockhart, Kirkwood and Harris [5] placed the requirement at the tenth month of pregnancy at three times that of the nonpregnant woman, and other investigators [6] have emphasized the greatly increased need for thiamine during pregnancy. Toverud,[4] referring to infants several months of age, stated that breast-fed infants usually do not excrete thiamine. In balance studies on infants less than 6 months old, Knott [7] found that an intake of less than 80 U.S.P. units (240 micrograms) per day resulted in consistently low quantities of thiamine in the urine. Later, in a second study,[8] thiamine was measured in four hour collections of urine before and after supplementation with the vitamin. The infants, who were between 7 and 22 weeks of age, had an average thiamine excretion per four hours of 3 micrograms without supplement and of 6.5 micrograms for the four hours after supplementation. Breast-fed babies excreted smaller amounts of thiamine than artificially fed babies.

---

2. (*a*) Elvehjem, C. A.: The Role of Intestinal Bacteria in Nutrition, J. Am. Dietet. A. **22**:959-963 (Nov.) 1946. (*b*) Salaam, A. A., and Leong, P. C.: Synthesis of Vitamin B_1 by Intestinal Bacteria of the Rat, Biochem. J. **32**:958-963 (June) 1938.

3. Emerson, G. A., and Obermeyer, H. G.: Non-Availability of Fecal Thiamine in Thiamine Deficiency, Proc. Soc. Exper. Biol. & Med. **59**:299-300 (June) 1945. Elvehjem.[2a] Salaam and Leong.[2b] Allibone, E. C., and Finch, E.: Measurement of the Nutritional Level of Thiamin in Children by the Estimation of the Urinary Excretion, Arch. Dis. Childhood **20**:169-175 (Dec.) 1945.

4. Toverud, K. U.: The Excretion of Aneurin in Pregnant and Lactating Women and in Infants, Ztschr. f. Vitaminforsch. **10**:255-267, 1940.

5. Lockhart, H.; Kirkwood, S., and Harris, R. S.: The Effect of Pregnancy and Puerperium on the Thiamine Status of Women, Am. J. Obst. & Gynec. **46**: 358-365 (Sept.) 1943.

6. King, G., and Ride, L. T.: The Relation of Vitamin B_1 Deficiency to the Pregnancy Toxaemias: A Study of Three Hundred and Seventy-One Cases of Beri-Beri Complicating Pregnancy, J. Obst. & Gynaec. Brit. Emp. **52**:130-147 (April) 1945.

7. Knott, E. M.: Determination of Vitamin B_1 Requirement of Infants by Means of Urinary Excretion of Thiamin, Proc. Soc. Exper. Biol. & Med. **45**: 765-766 (Dec.) 1940.

8. Knott, E. M.; Kleiger, S. C., and Schultz, F. W.: Is Breast Milk Adequate in Meeting the Thiamine Requirement in Infants? J. Pediat. **22**:43-49 (Jan.) 1943.

To supplement an investigation of the composition of human milk and the metabolism of women during the reproductive cycle,[9] analytic data were obtained on the concentrations of thiamine, riboflavin, nicotinic acid, N^1-methylnicotinamide chloride, calcium pantothenate and biotin in samples of urine from 24 infants during their first week of life. It was felt that if the urinary excretion of the vitamins could be taken as an indication of the nutritional status with respect to them there was need for this information in relation to late fetal and early neonatal life. The vitamin C excretion in the urine of newborn infants and the concentrations of ascorbic acid in the blood of the umbilical cord and in the blood of both the mothers and their breast-fed infants are presented in another paper.[10]

MATERIAL AND METHODS

Procedure.—Both white and Negro male infants were subjects of the study. The economic status of all the mothers was consistent with the private clinic fees of the hospital. They were in good health throughout an uncomplicated pregnancy, followed by a normal delivery. The infants were born during March, April and May and were entirely breast fed during the period in which urine was collected. They received the routine nursery care maintained by the pediatric staff for the obstetric division of the hospital. They were offered boiled water every four hours until the increasing supply of mother's milk resulted in cessation of the infant's desire for water. Each baby was put to the breast after the first twelve hours from birth at regular nursing periods except for the 2 a.m. feedings falling within the first forty-eight hours. Thereafter, the infant was permitted to nurse from both breasts for seven to ten minutes each, every four hours, or six feedings in twenty-four hours. The baby was weighed before and after each feeding to determine the milk intake. The mothers' diets were similar to those reported for the subjects of the studies on the composition of human milk.[11]

Specimens of urine were collected in small Erlenmeyer flasks. The neck of the flask was inserted through a slit in a square of adhesive tape, which held it securely over the penis. The specimens were obtained by the nursery staff as a part of their routine duties. Many of the collections probably represent twenty-four hour excretions, owing to the infrequency of urination and the small amounts of urine voided during the first seventy-two hours, although no attempt was made to obtain twenty-four hour collections.[12] Micturition begins by the fifth month

9. Macy, I. G.; Williams, H. H.; Pratt, J. P., and Hamil, B. M.: Human Milk Studies: XIX. Implications of Breast Feeding and Their Investigation, Am. J. Dis. Child. **70**:135-141 (Sept.) 1945.

10. Hamil, B. M.; Munks, B.; Kaucher, M.; Moyer, E. Z., and Williams, H. H.: Vitamin C in the Blood and Urine of the Newborn and in the Cord and Maternal Blood, Am. J. Dis. Child., to be published.

11. Kaucher, M.; Moyer, E. Z.; Williams, H. H., and Macy, I. G.: Adequacy of the Diets of Lactating Women as Determined by Analyses of Their Food and Breast Milk, J. Am. Dietet. A. **22**:594-601 (July) 1946.

12. The benefit to be derived from twenty-four hour collections, involving painstaking care and full time supervision of the nurses, seemed offset by the desirability of having the infant nursed at the breast without anxiety on the part of the mother, so that stimulation of milk flow was uninhibited.

of gestation,[13] or possibly before,[14] so that indeterminable quantities of urine are contributed to the amniotic fluid. Many infants urinate during delivery or immediately after, but in some instances the first collections may represent urine accumulated in the bladder before labor began.

Handling of Specimens.—When a specimen flask was removed from an infant, 2 cc. of urine was removed for determination of the vitamin C content. The remainder of the specimen was transferred to an amber bottle, to prevent the destruction of riboflavin by light, and placed in the refrigerator. Once each day all the specimens collected were taken to the laboratory, where sufficient glacial acetic acid was added to make a 2 per cent solution. The samples were stored at −50 F. until the analyses could be made. Previous experience had shown that the concentration of the B complex vitamins was not affected in this period of storage.

Methods.—The concentrations of thiamine, riboflavin and N^1-methylnicotinamide, a metabolic end product of nicotinic acid, were determined chemically on the same aliquot of urine. The aliquot was passed through an activated "decalso" [15] column, collected quantitatively with the first 10 cc. of wash water, then used for determination of riboflavin by the procedure of Conner and Straub,[16] using "florosil" as the adsorbent. Both N^1-methylnicotinamide and thiamine are adsorbed on "decalso" and are eluted by potassium chloride. Thiamine was determined by the thiochrome method of Hennessy,[17] with the sulfite blank suggested by Mason and Williams [18] and with further modification.[19]

To produce fluorescence of N^1-methylnicotinamide, the thiochrome procedure was followed with one modification. Instead of alkaline ferricyanide, 3 cc. of 15 per cent sodium hydroxide was added to an aliquot of 5 cc. of the acid potassium chloride eluate from the "decalso" column. The N^1-methylnicotinamide was measured against quinine sulfate as a standard. Later, the quinine sulfate standard was compared with known amounts of N^1-methylnicotinamide chloride [19a] in solu-

13. Campbell, M. F.: Pediatric Urology, New York, The Macmillan Company, 1937, vol. 1.

14. Cameron, G., and Chambers, R.: Direct Evidence of Function in Kidney of an Early Human Fetus, Am. J. Physiol. **123**:482-485 (Aug.) 1938.

15. "Decalso" is a zeolite obtained from the Perumtit Company, New York.

16. Conner, R. T., and Straub, G. J.: Combined Determination of Riboflavin and Thiamine in Food Products, Indust. & Engin. Chem. (Anal. Ed.) **13**:385-388 (June 15) 1941.

17. Hennessy, D. J.: A Standard Thiochrome Assay for the Determination of Thiamin in Cereal Products, Cereal Chem. Bull. **2**:25-29 (May 1) 1942.

18. Mason, H. L., and Williams, R. D.: Determination of Thiamine in Urine by the Thiochrome Method: Estimation of the Blank, J. Biol. Chem. **146**:589-594 (Dec.) 1942.

19. Roderuck, C. E.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXIII. Free and Total Thiamine Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:162-170 (Sept.) 1945.

19a. Huff and Perlzweig [31] reported the isolation of "N^1-methylnicotinamide chloride" and so referred to the substance in reporting a method for determining N^1-methylnicotinamide in urine. The method used in this work is based on their publication, and the standard solution was made with "N^1-methylnicotinamide"

(Footnote continued on next page)

tion, and a factor was obtained for converting our results into units of this compound. One microgram of quinine sulfate was equivalent to 32 micrograms of N^1-methylnicotinamide chloride in our procedure. Maximum fluorescence of N^1-methylnicotinamide in isobutanol was not always attained within twenty minutes, the time limit suggested by Najjar and Wood[20]; so readings were taken at intervals of up to an hour until they became constant.[21]

The quantity of urine required for the three chemical determinations was an aliquot of 3 to 8 cc. Since this amount was not always available, fewer data were collected for N^1-methylnicotinamide than for the other vitamins. In some cases, duplicate determinations were not possible.

It had been noted in an earlier study with adult urine[22] that the concentration of riboflavin seemed to decrease during even the short period of storage in that study. However, when aliquots of stored urine were incubated with clarase before the chemical determinations were made, results equivalent to those found with fresh urine could be obtained. In the microbiologic assays made on stored urine, filtered samples gave lower concentrations of riboflavin than unfiltered ones. Since urine contains a considerable amount of sediment, it appeared likely that the riboflavin formed a loose combination with some of the precipitated material. The sediment usually increased during storage of samples; so the combination may have occurred during precipitation. Because of this phenomenon, all samples were incubated with clarase before chemical determinations were made.

Riboflavin, nicotinic acid, pantothenic acid and biotin in the infants' urine were determined microbiologically, using the organism Lactobacillus arabinosus and the general procedure described in a previous paper.[23] The basal medium employed in the assays of nicotinic acid and biotin was a modification of that used by Krehl, Strong and Elvehjem,[24] while the medium used in the assay of pantothenic acid was a modification of the one suggested by Strong, Feeney and Earle.[25]

---

provided by Dr. Perlzweig, according to his instructions. The method used with the urine of the infants has been discussed (Coryell, M. N.; Roderuck, C.; Harris, M. E.; Miller, S.; Rutledge, M. M.; Williams, H. H., and Macy, I. G.: Metabolism of Women During the Reproductive Cycle: XIII. The Utilization of Niacin During Lactation, J. Nutrition **34**:219-231 [Aug.] 1947).

20. Najjar, V. A., and Wood, R. W.: Presence of a Hitherto Unrecognized Nicotinic Acid Derivative in Human Urine, Proc. Soc. Exper. Biol. & Med. **44**: 386-390 (June) 1940.

21. The filters were the ones used to measure the thiochrome fluorescence and the instrument used for all three chemical determinations was the Coleman photofluorometer.

22. Roderuck, C.; Coryell, M. N.; Williams, H. H., and Macy, I. G.: Metabolism of Women During the Reproductive Cycle: IX. The Utilization of Riboflavin During Lactation, J. Nutrition **32**:267-283 (Sept. 10) 1946.

23. Coryell, M.; Harris, M. E.; Miller, S.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXII. Nicotinic Acid, Pantothenic Acid, and Biotin Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:150-161 (Sept.) 1945.

24. Krehl, W. A.; Strong, F. M., and Elvehjem, C. A.: Determination of Nicotinic Acid, Indust. & Engin. Chem. (Anal. Ed.) **15**:471-475 (July 15) 1943.

25. Strong, F. M.; Feeney, R. E., and Earle, A.: Microbiological Assay for Pantothenic Acid, Indust. & Engin. Chem. (Anal. Ed.) **13**:566-570 (Aug. 15) 1941.

The basal medium in the determination of riboflavin was similar to the one described by Strong and Carpenter,[26] but modified by the addition of glutamic acid hydrochloride (40 mg.), dextrose (1 Gm.) and sodium acetate (0.4 Gm.). These quantities were added to each 100 cc. of undiluted medium over and above the original amounts used in Strong and Carpenter's medium. Yeast solution (1 cc.), prepared by exposing a 5 per cent solution of "difco" yeast extract at p_H 9 to ultraviolet radiation for four to five hours, was also added. The p_H of the medium was adjusted to from 6.2 to 6.4, instead of the usual 6.6 to 6.8 before it was pipeted into the assay tubes. The samples of urine were neutralized to a p_H of 6.5 to 6.8 and diluted, without filtering, to concentrations suitable for the various assays.[27] Duplicate determinations were made when volume permitted.

RESULTS OF STUDY

The concentrations of the B complex vitamins in the urine of newborn infants are given in table 1 for each consecutive twenty-four hour

TABLE 1.—*Concentration of Vitamins of the B Complex* in Urine of Newborn Infants*

Age, Days		Thiamine	Riboflavin		N^1-methylnicotinamide	Nicotinic Acid	Pantothenic Acid	Biotin
			Chemical	Microbiologic				
1	Number of samples †	10	10	14	10	13	14	14
	Concentration	9	119	140	2,640	58	86	3
2	Number of samples	4	4	15	4	5	15	14
	Concentration	9	120	79	3,820	128	171	4
3	Number of samples	5	5	16	5	10	17	17
	Concentration	13	40	34	1,820	67	213	3
4	Number of samples	3	3	16	3	8	16	16
	Concentration	10	14	9	1,440	62	198	1
5	Number of samples	5	5	8	5	8	8	8
	Concentration	4	6	4	710	30	109	0
6	Number of samples	1	1	4	1	4	4	4
	Concentration	1	2	1	120	16	73	0
7	Number of samples	1	1	6	1	5	6	6
	Concentration	0	2	2	60	14	99	0

* Values are expressed in micrograms per hundred cubic centimeters.
† Some of the samples were not sufficient for determination of all the vitamins. The scatter of analyses was influenced by concentration of attention on the first four days and the necessity for staggering the collections to conform with available working time.

period during the first week after birth. Twenty-nine samples of urine from 16 babies were assayed chemically for thiamine, riboflavin and N^1-methylnicotinamide. Microbiologic assays were done on 79 samples from 24 babies for riboflavin, 53 samples from 23 babies for nicotinic acid, 80 samples from 24 babies for pantothenic acid and 79 samples from 24 babies for biotin.

26. Strong, F. M., and Carpenter, L. E.: Preparation of Samples for Microbiological Determination of Riboflavin, Indust. & Engin. Chem. (Anal. Ed.) **14:** 909-913 (Nov. 15) 1942.

27. The growth response of the organisms to the vitamins was measured by turbidity readings on the Cenco Sheard photolometer. Since values obtained by titration of acid produced were similar to those obtained by turbidity readings, no advantage would have been gained by employing the longer titration method.

The average concentration of thiamine in the urine was maximal on the third day after birth (13 micrograms per hundred cubic centimeters); thereafter it declined rapidly. The range of concentrations during the first four days was rather wide, 2.3 to 21.2 micrograms per hundred cubic centimeters. Specimens collected from the same infant varied considerably. The average, 8.3 micrograms per hundred cubic centimeters, is lower than that reported by Neuweiler.[1] His highest value was 105 micrograms per hundred cubic centimeters, though the average milk intake (248 cc. a day) of the infants he studied is comparable to that of the infants in the present study, 268 cc. However, the concentration of thiamine as such in the urine is not an indication of thiamine nutrition, for the vitamin may be destroyed during the metabolic processes and excreted as pyrimidine and thiazole fractions of the original molecule. Only free thiamine is represented by these urinary values.

The average concentration of riboflavin showed a striking decrease during the first three days after birth, declining to a relatively insignificant amount by the fifth day. The values for the microbiologic assays and the chemical determinations showed similar trends. The microbiologic values for all but 1 of the 29 samples analyzed by both methods were lower than the chemical values. Neuweiler [28] also observed a wide range of values for twenty-four hour excretions of riboflavin by 18 male infants on the ninth and tenth days of life. The range was from 22 to 207 micrograms per day, with an average of 87 micrograms. He saw no relation between excretion and development, or diet, and attributed the wide spread of his values to variable storage of riboflavin during intrauterine life.

The concentrations of nicotinic acid rose slightly during the second twenty-four hour period, then slowly decreased until the sixth or seventh day, when they were somewhat below the rather uniform level found in normal adult urine (20 to 60 micrograms per hundred cubic centimeters). The average for the second twenty-four hour period was influenced by an unusually high value, 258 micrograms per hundred cubic centimeters, in 1 of the 5 samples assayed. The values for nicotinic acid alone in urine, however, have little significance, since the ingestion of the acid or its amide results in an increase in the excretion of N^1-methylnicotinamide, and not of nicotinic acid or of nicotinamide.[29] The methylated compound is believed, therefore, to be the major end product of nicotinic acid metabolism, although there are probably other

28. Neuweiler, W.: Ueber den Flavinstoffwechsel beim Neugeborenen, Ztschr. f. Vitaminforsch. **6**:316-324 (Oct.) 1937.

29. Huff, J. W., and Perlzweig, W. A.: A Rapid Method of Estimating N^1-Methylnicotinamide in Urine, J. Biol. Chem. **150**:483-484 (Oct.) 1943. Ellinger, P., and Coulson, R. A.: The Urinary Elimination of Nicotinamide by Man, Biochem. J. **38**:265-270, 1944. Coulson, R. A., and Stewart, C. A.: Metabolism of

compounds which have not been identified.[30] Before its positive chemical identification,[31] N^1-methylnicotinamide was designated as factor F_2, a substance which gave a bluish fluorescence in the presence of alkali and was extractable with butyl or isobutyl alcohol. The fluorescent substance measured by Najjar and associates [32] is believed to be the alkyl ether of the carbinol of N^1-methylnicotinamide. However, it was measured and is recorded in table 1 as N^1-methylnicotinamide chloride. The values for the first three or four days were considerably higher than those for normal adult urine (0 to 10 micrograms per cubic centimeter), but decreased to low levels by the fifth or sixth day. The high values observed for the urine of newborn infants are similar to those for the urine of adults after administration of nicotinic acid or nicotinamide.[29]

The average concentrations of pantothenic acid increased during the second and third days after birth, decreasing to approximately the level of the first day on the sixth and seventh days post partum. The average values for biotin show relatively high concentrations on the first two or three days, decreasing to very low levels by the fifth day of life.

For comparison, the values given in table 1 are plotted in chart 1, together with the concentrations of the same vitamins in human milk.[33] It is evident that during the period of secretion of colostrum, notwithstanding the infants' small intake of milk, of low vitamin content, the concentrations of the vitamins in the urine are high, dropping to low levels by the fifth day post partum.

Owing to the small amounts of breast milk secreted, a baby's daily intake of vitamins is small during the colostral period. From a state of starvation on the first day, there are rapid increases in the amounts of vitamins obtained from breast feedings. These increases may be attributed not only to the increasing milk flow but also to the rising concentrations of the vitamins in the milk.

Values for the twenty-four hour urinary excretions of the various vitamins of the B complex for each day of the first week of life were

Nicotinamide, Nicotinic Acid and Diethylamide of Nicotinic Acid (Coramine) by Newborn and Premature Infants, Proc. Soc. Exper. Biol. & Med. **61**:364-369 (April) 1946.

30. Mickelsen, O., and Erickson, L. L.: The F_2 Excretion of Normal Men on Different Levels of Niacin Intake, Proc. Soc. Exper. Biol. & Med. **58**:33-36 (Jan.) 1945.

31. Huff, J. W., and Perlzweig, W. A.: N^1-Methylnicotinamide, a Metabolite of Nicotinic Acid in the Urine, J. Biol. Chem. **150**:395-400 (Oct.) 1943.

32. Najjar, V. A.; White, V., and Scott, D. B. M.: On Isolation and Properties of Fluorescent Factor F_2 from Human Urine, Bull. Johns Hopkins Hosp. **74**:378-391 (June) 1944.

33. Roderuck, C. E.; Coryell, M. N.; Williams, H. H., and Macy, I. G.: Human Milk Studies: XXIV. Free and Total Riboflavin Contents of Colostrum and Mature Human Milk, Am. J. Dis. Child. **70**:171-175 (Sept.) 1945. Roderuck, Williams and Macy.[19] Coryell and others.[23]

estimated by multiplying the concentration by the daily output of urine, based on the values for volume percentages given in the literature.[34] On the third day post partum the average intake for the infants was 1½ ounces (49.35 cc.) per feeding, and on the seventh day the average intake was approximately 3 ounces (88.74 cc.) at each feeding. The average daily total fluid intake (milk plus water) of this group of infants was greater than that reported previously;[34] therefore the computed volumes of urine were proportionately higher.

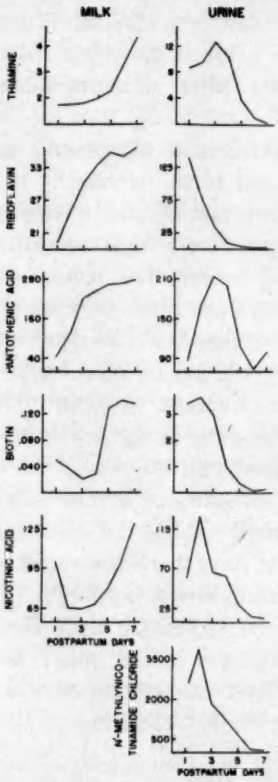


Chart 1.—Concentrations of thiamine, riboflavin, pantothenic acid, biotin, nicotinic acid and N^1-methylnicotinamide chloride in the breast milk intake and in the urinary excretion of infants during the first seven days of life.

The vitamin intake of the infants was calculated from the weight of the breast milk consumed during each twenty-four hour period, using the concentrations for respective days post partum obtained by analyses of milk secreted by mothers receiving a similar diet under

34. Reusing, H.: Beiträge zur Physiologie des Neugeborenen, Ztschr. f. Geburtsh. u. Gynäk. **33**:36-93, 1895. Thomson, J.: Observations on the Urine of the Newborn Infant. Arch. Dis. Childhood **19**:169-177 (Dec.) 1944.

comparable conditions.[83] Obviously, data from calculations involving such assumptions are only rough approximations, but the trends of the average daily intakes and excretions of vitamins, as plotted in chart 2, are significant.

The excretion of the vitamins (except pantothenic acid) in the urine was relatively high on the first, second and third days, when there were rapid loss of weight and relatively small intake of milk. By the seventh day, the intake of milk was abundant and the babies had almost regained the weight at birth. This early excretion of the vitamins, particularly on the first day, when little milk is consumed, and on the second and third days, during the period of initial loss of

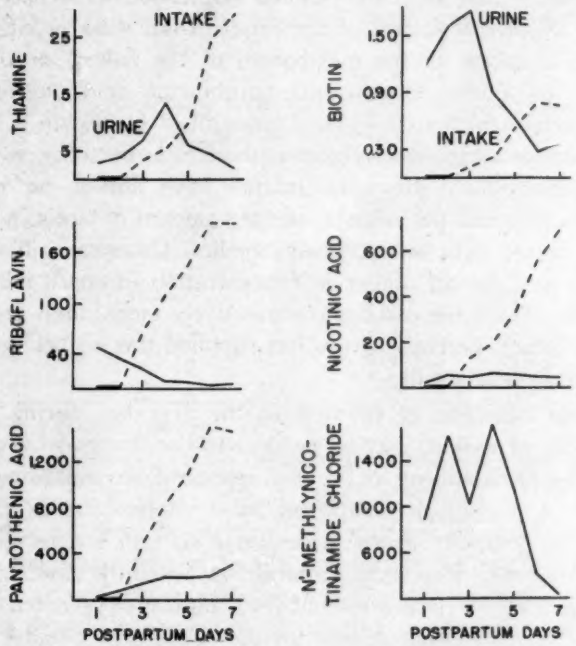


Chart 2.—Estimated daily intakes of thiamine, riboflavin, pantothenic acid, biotin, nicotinic acid and N^1-methylnicotinamide chloride from breast milk and amounts excreted in the urine by infants during the first seven days of life.

weight, is significant and must represent tissue storage during intrauterine development. After this time, when the infants are regaining lost weight and the intake of vitamins and other nutriments is increasing notably, there are marked decreases in the concentrations of vitamins in the urine, resulting in a rapidly widening gap between the intakes and the urinary excretions.

COMMENT

It is doubtful whether the increasing gap between the intake and the urinary output of the B complex vitamins during the period of

rapid gain in weight is an indication of the extent to which these vitamins are concerned with the active metabolic state accompanying the rapid growth of the neonatal period. Oser, Melnick and Hochberg [35] obtained evidence that in the normal adult thiamine shows a variable stability in the gastrointestinal tract prior to absorption. It would seem that this variability would be less likely to exist when the vitamin is in its natural state in the milk ingested directly from the mother's breast. However, this explanation may need consideration with respect to all the vitamins of the B complex.

Thiamine, riboflavin and nicotinic acid are all recognized as integral parts of certain coenzymes, which, in turn, function in the oxidative enzyme systems that facilitate cellular respiration as a part of tissue physiology. Little is known of the fundamental roles of either pantothenic acid or biotin in the metabolism of the animal or the human organism. In animal experiments pantothenic acid deficiencies are more conspicuous in the young, and impairment of growth is frequently one of the major symptoms. Biotin is thought to be active in extremely small concentrations. Newborn infants have almost no reserve of biotin in the liver and the kidneys, and the amount of biotin in colostrum and early breast milk is extremely small. Thiamine, riboflavin and pantothenic acid are all higher in concentration in cow's milk than in human milk. Since the calf has comparatively more rapid growth than the human infant, perhaps nature has supplied this higher requirement of vitamins in cow's milk.

The large excretion of vitamins on the first day, during starvation and rapid loss of weight, may be incident to the change from an aquatic to a gaseous environment, or it may represent an unloading required to maintain a physiologic balance of these vitamins in the tissue cells following the change from the intrauterine state of low oxygen tension in a fluid environment to an environment in which the gaseous exchange through the lungs and skin establishes a higher oxygen tension and a different physiologic environment for the tissue cells obtains. In their roles as catalyzers of cell respiration this would seem a logical possibility. In the human fetal liver, Neuweiler [36] found 4 to 8 micrograms of riboflavin per gram, of which 52 to 87 per cent was bound, as against 1 to 2 micrograms per gram in the placenta, of which only 35 to 54 per cent was bound. It is likely that the variable accumulation of the vitamins in the fetal tissues may depend on changes in p_H, oxygen

35. Oser, B. L.; Melnick, D., and Hochberg, M.: Physiological Availability of the Vitamins: Study of Methods for Determining Availability of Vitamins in Pharmaceutical Products, Indust. & Engin. Chem. (Anal. Ed.) **17**:405-411 (July) 1945.

36. Neuweiler, W.: Der Gehalt fröntaler Organe (Leber, Placenta) an Flavinen, Ztschr. f. physiol. Chem. **249**:225-230, 1937.

tension, colloidal content, osmotic pressure and other physical factors, of which alterations at birth result in the excretion of vitamins during the first few days post partum. Renal function begins at 9 weeks in the human fetus and is continuous, but slow. The visceral layer of Bowman's capsule forms a heavy sac, which confines the glomerular tufts and serves as an impediment to rapid glomerular elimination. Windle [37] implied that this situation may be a safeguard against a serious disturbance of the fluid balance in utero. At birth, when placental elimination is suddenly abolished, these columnar epithelial investments of the renal glomeruli burst and glomerular filtration is thenceforth greatly enhanced. This purely physiologic change in the kidney at birth may be the only explanation necessary for the urinary excretion in such high concentration of these vitamins by newborn infants.

TABLE 2.—*Average Daily Fluid Intake of Twenty-Four Infants During the First Week of Life*

Interval Post Partum, Days	Body Weight,* Gm.	Breast Milk, Cc.	Total Fluid, Cc.
1	3,407	1	158
2	3,397†	5	203
3	3,407	216	266
4	3,432	345	365
5	3,463	407	415
6	3,483	463	472
7	3,518‡	450	465

* Average weight at birth, 3,595 Gm.
† Average initial loss of weight, 198 Gm.
‡ Average daily gain, 23 Gm.; the average weight at this time was 82 Gm. less than the average weight at birth.

In pediatric practice, the giving to newborn infants of ample amounts of water to counteract loss of weight and hunger (thirst), pending the establishment of milk flow and between the regular feeding periods, has replaced the older procedure of offering the breast whenever the infant showed signs of hunger. The values in table 2 show the average daily milk intake, the average total fluid intake and the average daily weight of the infants studied for the first seven days post partum. Whether the postpartum loss in weight was reduced by the large intakes of water during the first few days after birth cannot be determined. The establishment and maintenance of lactation have been shown to depend on stimulation of the breasts; [38] however, the mothers of the infants in this study were in an environment favorable to breast feeding,

37. Windle, W. F.: Physiology of the Fetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders Company, 1940.

38. Davies, V., and Pratt, J. P.: The Stimulation and Maintenance of Lactation, Am. J. Nursing **46**:242-244 (April) 1946.

and the average daily milk production was higher than that of the mothers in earlier studies.[39] The decreasing concentrations of vitamins in the urine (chart 1) might indicate that water intake does not alter the physiologic trend of vitamin excretion during the first week post partum. However, as early as 1930, Cowgill, Rosenberg and Rogoff [40] showed in their experiments with dogs receiving vitamin B–free diets that large amounts of fluid administered orally "shortened by one-half the time of appearance of anorexia." The possibility that in the newborn infant large amounts of water may produce a "washing out" of the water-soluble vitamins emphasizes the need for further investigation of the interrelations between the daily intake and excretion of vitamins and those of fluid, both ante partum and post partum.

SUMMARY

The concentrations of thiamine, riboflavin, nicotinic acid, N^1-methylnicotinamide, calcium pantothenate and biotin were determined in urine from 24 healthy white and Negro male infants during their first week of life.

The maximal average concentrations of thiamine (13 micrograms per hundred cubic centimeters) and of pantothenic acid (213 micrograms per hundred cubic centimeters) were found in the urine excreted on the third day of life; the maximal average value for riboflavin (140 micrograms per hundred cubic centimeters) was found on the first day; and the maximal average concentrations of nicotinic acid (128 micrograms), N^1-methylnicotinamide (3,820 micrograms) and biotin (4 micrograms per hundred cubic centimeters), on the second day. By the seventh day the average concentrations had declined to 0 micrograms, for thiamine; 2 micrograms, for riboflavin; 14 micrograms, for nicotinic acid; 60 micrograms, for N^1-methylnicotinamide; 99 micrograms, for pantothenic acid, and 0 micrograms, for biotin.

Estimation of the daily excretion of the vitamins indicated that secretion into the urine was high during the first three days, when the loss of weight was rapid and the intake of vitamins small. As the supply of breast milk increased, excretion of vitamins in the urine continued to decrease. The large amounts excreted early in life apparently represent tissue storage during intrauterine development and reduction of the stores in response to changes resulting from the transition to the extrauterine environment.

660 Frederick Street.

---

39. Macy and others.[9] Kaucher and others.[11]

40. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: The Physiology of Vitamins: XIV. The Effect of Administration of Large Amounts of Water on the Time Required for Development of the Anorexia Characteristic of a Deficiency of the Vitamin-B Complex, Am. J. Physiol. **95**:537-541, 1930.

PENICILLIN IN TREATMENT OF EMPYEMA IN CHILDREN

GEORGE E. PRINCE, M.D.
GASTONIA, N. C.
AND
WILLIAM J. TEMPLE, M.D.
LOUISVILLE, KY.

THORACIC empyema has been treated by surgical drainage [1] for many years, and until the advent of penicillin other methods of therapy were comparatively ineffective. Even with the use of the sulfonamide compounds surgical drainage was still believed paramount.[2] The intrapleural and parenteral use of penicillin has recently reduced the necessity for surgical intervention.[3] Although the results have been satisfactory in many instances, certain limitations have been noted. Recurrence [4] of the empyema and failure to eliminate the cavity after sterilization [5] have been reported. The incidence of these and other sequelae can be reduced if proper evaluation of the case is made before treatment is begun. Hirshfeld and associates [6] established the following conditions as necessary for successful treatment of empyema with penicillin: The causative organism must be susceptible to penicillin; it must be possible for the penicillin instilled into the empyema cavity to come into contact with the organism; the cavity must not contain pieces of necrotic lung tissue or large clots of fibrin; no anatomic condition, such as bronchial fistula, which can cause reinfection of the cavity or allow the penicillin to escape, may be present; the lung must be capable of reexpanding.

From the Department of Pediatrics, University of Louisville School of Medicine.

1. Williams, M. H.: Postpneumonic Empyema in Infants and Children, J. Thoracic Surg. **12**:160-185 (Dec.) 1942.

2. Forbes, G. B.: The Diagnosis and Management of Severe Infection in Infants and Children: A Review of Experiences Since the Introduction of Sulfonamide Therapy; V. Staphylococcal Empyema, J. Pediat. **29**:45-67 (July) 1946.

3. Brown, B.; Ory, E. M.; Meads, M., and Finland, M.: Penicillin Treatment of Empyema (Review of Literature), Ann. Int. Med. **24**:343-370 (March) 1946.

4. Butler, E. C. B.; Perry, K. M. A., and Valentine, F. C. O.: Treatment of Acute Empyema with Penicillin, Brit. M. J. **2**:171-175 (Aug. 5) 1944.

5. Poppe, J. K.: Limitation of Penicillin in Treating Empyema, J. A. M. A. **129**:435-438 (Oct. 6) 1945.

6. Hirshfeld, J. W.; Buggs, C. W.; Abbott, W. E., and Pilling, M. A.: The Value of Penicillin in the Treatment of Empyema, J. A. M. A. **128**:577-582 (June 23) 1945.

Although more than 275 cases of empyema treated with penicillin have been collected from the literature,[7] only a small number were of children. In the following cases from the Children's Hospital of Louisville, penicillin therapy was used.

REPORT OF CASES

CASE 1.—B. R., a 2 year old white boy, was admitted to the hospital on May 7, 1944. He was believed to have had pneumonia for the past three weeks. Sulfonamide drugs had been administered, but no improvement in his condition was noted. The patient had been cyanotic a few hours before he arrived at the hospital.

His temperature was 100 F., and he was in serious respiratory distress when first seen. The entire right side of the thorax was flat to percussion, and breath sounds were absent on this side. A roentgenogram of the chest (fig. 1) revealed increased density on the right side. The heart rate was rapid, and a gallop rhythm

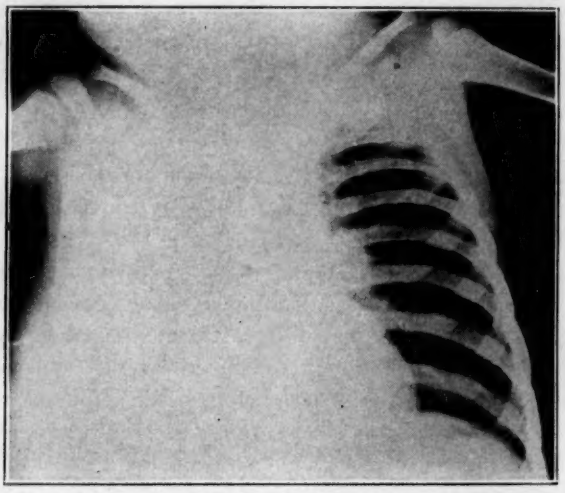


Fig. 1 (case 1).—Roentgenogram of the chest made on the patient's admission to the hospital, showing abnormal density on the right side.

was present. The left external auditory canal contained a purulent discharge, and the tympanic membrane was inflamed.

A thoracentesis performed on admission to the hospital revealed 250 cc. of greenish material, from which Pneumococcus type I was isolated. Treatment was started with sulfathiazole sodium given subcutaneously, and was continued for seven days. Penicillin, 20,000 units, was then given intramuscularly every three hours for eight days. Thoracentesis was done daily for six days, and 20,000 units of penicillin was instilled each time. After the third intrapleural injection, no more fluid could be obtained.

He responded well to the therapy, and his temperature remained normal after the eighth day. He was discharged on the twentieth day from the hospital, appar-

7. Ory, E. M.: The Treatment of Empyema with Penicillin, Am. Practitioner **1**:23-26 (Sept.) 1946.

ently well. At the time of discharge there was still some haziness in the right lower pulmonary field.

CASE 2.—J. S., a 2½ year old white boy, was admitted on June 10, 1944, with a history of pain in the abdomen and fever of three days' duration. No cough or dyspnea had been present. The only previous treatment had been administration of a cathartic. On admission his temperature was 103 F., and he appeared acutely ill. The breath sounds were exaggerated over both pulmonary fields, but no change was found on percussion. There was an abscess on the left shoulder. Examination of the abdomen revealed no abnormalities. The roentgenogram of the chest at this time showed consolidation in the middle lobe of the right lung with adenopathy of the left hilus.

A diagnosis of pulmonary abscesses was considered, and the patient was given sulfadiazine for three days, without improvement. At this time dulness to percussion was noted over the lower lobe of the left lung both anteriorly and posteriorly. The medication was changed to sulfapyridine and later to sulfathiazole, without improvement. On the fifth day in the hospital a thoracentesis was performed on the left lung and 20 cc. of thick purulent material was aspirated. The chemotherapy was discontinued and 10,000 units of penicillin was given intramuscularly every three hours. Improvement was noted on the following day, and the patient's temperature fell below 100 F. on the third day of penicillin therapy. Treatment with penicillin was continued for fifteen days. Another thoracentesis was done two days after the first, and a small amount of purulent fluid was obtained. No penicillin was instilled into the pleural cavity. Cultures of the fluid obtained on both occasions yielded Staphylococcus aureus in pure culture. Cultures of the blood revealed no pathogens. Fluid was still seen roentgenographically in the left pleural cavity two days after the final thoracentesis, but this condition gradually disappeared.

The patient became afebrile during the second week in the hospital, but several furuncles developed in the fourth week and the temperature again became elevated. Prolongation of hospitalization to forty-nine days was partly due to this complication.

Examination after discharge revealed that the patient's lungs were clear, with no evidence of fluid.

CASE 3.—E. E., a 5 year old white boy, was admitted to the hospital on Sept. 10, 1944. He had had pain in the left side of the chest, fever, cough and dyspnea for thirteen days. One of the sulfonamide compounds had been given him for seven days prior to his entrance to this hospital.

His temperature on admission was 101 F., and he had severe respiratory distress. The left side of the thorax was flat to percussion, and breath sounds were absent on this side. The mediastinum was shifted to the right. There was edema of the feet and ankles. A roentgenogram of the chest confirmed the clinical impression of massive pleural effusion on the left side.

A thoracentesis was performed immediately and 850 cc. of greenish fluid was removed. Penicillin, 2,500 units, was instilled intrapleurally, and 5,000 units was given intramuscularly every three hours for the next nine days. Thoracentesis was repeated four times, and 10,000 units of penicillin was placed in the cavity each time. Pneumococcus type V was obtained from the first tap, but cultures made after the third day in the hospital yielded no organisms.

He continued to improve and penicillin was not given after the eleventh day of hospitalization. Four days after the medication was discontinued the patient was removed from the hospital by his father, against the advice of the medical staff. The patient appeared well at this time, but breath sounds were still slightly dimin-

ished on the left side. We have not received information concerning this patient since his removal from the hospital.

CASE 4.—R. W., a boy aged 5 weeks, was admitted to the hospital on Jan. 11, 1945. He had had a cough for two weeks and dyspnea for the past three days. The child had not been well since birth and had had diarrhea and signs of malnutrition. He had become cyanotic and critically ill the day he was brought to the hospital.

At that time his temperature was normal, and it remained so throughout his stay in the hospital. He was cyanotic and in severe respiratory distress. His weight was 6 pounds 14 ounces (3,119 Gm.). Sternal retraction was pronounced. There was dulness to percussion in the base of the right lung, and breath sounds were diminished in this area. A roentgenogram of the chest showed increased density of the entire right side.

Penicillin, 2,500 units, was given every three hours for twenty days, and 10,000 units was given intrapleurally on two occasions. Purulent material was obtained when thoracentesis was done, and cultures yielded Staph. aureus. The patient recovered quickly from his infection, but because of poor nutrition he remained in the hospital for thirty-eight days.

CASE 5.—P. O., a girl aged 3 years, was admitted to the hospital on Feb. 19, 1945. She had been coughing for three weeks and had had pain in the left side of the chest for one week. She had received no medication prior to admission.

Her temperature was 103 F., but she did not appear acutely ill. There was dulness to percussion over the left side of the thorax, and breath sounds were diminished in this area. A roentgenogram of the chest showed the left side to be cloudy.

The patient was given 5,000 units of penicillin every three hours. A thoracentesis was performed on admission, and 150 cc. of straw-colored fluid was removed. No penicillin was injected intrapleurally until seven days later, when cloudy fluid was recovered. Only 5,000 units of penicillin was given intrapleurally. Cultures of the fluid yielded no organism. On the third day in the hospital, after the intramuscular injection of penicillin was discontinued, sulfadiazine was administered orally. She responded rapidly, and the temperature returned to normal on the eleventh day in the hospital. She was discharged seven days later and has remained well since that time.

CASE 6.—E. C., a 6 month old white girl, was admitted to the hospital on April 30, 1946. She had had a sore throat, fever and vomiting for four days. A private physician had made a diagnosis of pneumonia and had prescribed a "liquid medicine." At the time of admission her temperature was 104 F. and she exhibited moderate dyspnea. Examination of the chest revealed limited expansion, bronchial breathing and a flat percussion note on the left side. A roentgenogram of the chest (fig. 2*A*) revealed partial consolidation in the left pulmonary field. Penicillin therapy, 20,000 units given intramuscularly every three hours, was instituted on the day of admission.

The child improved somewhat but remained febrile and dyspneic. On the fifth day in the hospital a thoracentesis was done and 45 cc. of thick, green, purulent fluid was obtained. Fifty thousand units of penicillin in 10 cc. of isotonic solution of sodium chloride was instilled into the pleural cavity. Culture of the fluid revealed Staph. aureus. Six more thoracenteses were performed during the next nine days, and each time 50,000 units of penicillin in 10 cc. of isotonic solution of sodium chloride was given intrapleurally. The fluid from the second thoracentesis also showed Staph. aureus, but cultures of the fluid obtained thereafter yielded no organisms. Also, with each successive thoracentesis the fluid became less purulent

and smaller in amount. Serial roentgenograms of the chest revealed decreasing amounts of fluid, and on the sixteenth day in the hospital there was no definite evidence of fluid. The patient was discharged on the eighteenth day of hospitalization. Penicillin, 20,000 units every three hours, was administered intramuscularly during the entire period of hospitalization.

Follow-up studies were made, and, except for a thickened pleura on the left side, examination and roentgenograms of the chest showed nothing abnormal (fig. 2 *B*).

CASE 7.—F. B., a 5 year old white girl, was admitted on Feb. 19, 1946. She had had pain in the chest for ten days and fever for nine days. A diagnosis of pneumonia was made by the family physician and sulfadiazine therapy instituted. The symptoms disappeared temporarily but returned; in addition, abdominal pain, vomiting and anorexia had been present seven days. Examination revealed a temperature of 103 F. and she was dyspneic. Examination of the chest revealed faint breath sounds on the left side with hyperresonance on percussion above the third rib and dulness below that point. A roentgenogram of the chest (fig. 3 *A*) showed pneumothorax on the left side, with several fluid levels on the same side.

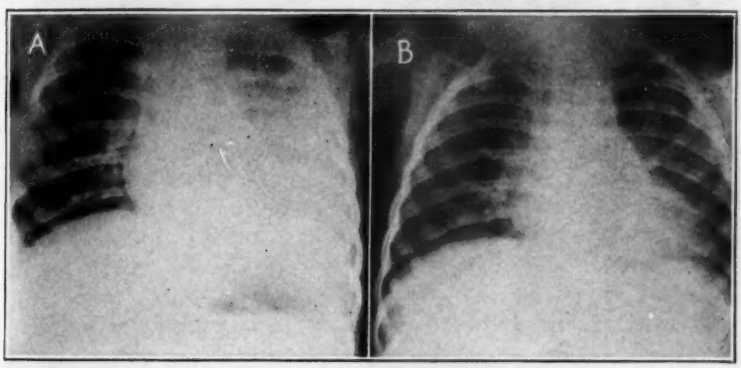


Fig. 2 (case 6).—*A*, roentgenogram of the chest made on the child's admission to the hospital, showing partial consolidation of the left lung; *B*, roentgenogram of the chest made on her discharge from the hospital, showing the left lung to be normal except for thickened pleura.

A thoracentesis was done and 30 cc. of a fibrinous, straw-colored fluid was removed. Fifty thousand units of penicillin in 20 cc. of isotonic solution of sodium chloride was instilled into the pleural cavity. No growth was obtained on culture of the fluid. Fifteen thousand units of penicillin was administered every three hours intramuscularly.

During the next two weeks four thoracenteses were performed, and each time cloudy, purulent fluid was removed, as well as varying amounts of air. Fifty thousand units of penicillin was instilled each time. Cultures of the fluid yielded no organisms.

On the fifteenth day in the hospital exploration of the left thoracic cavity was made by Dr. Hugo Polderman. A large amount of air, pus and fibrin was encountered, which was removed. The lung, covered with a thick fibrinous layer, was collapsed against the mediastinum. In the upper lobe an area of necrosis was observed, which was thought to be an abscess. Positive pressure was used to expand the lung. On the second postoperative day signs of obstruction of the respiratory

tract developed and a bronchoscopic examination was made. A mass of purulent material was aspirated from the subepiglottic region, but the trachea and bronchi appeared normal. On the following day, and also two days later, the procedure had to be repeated.

On the tenth postoperative day a thoracentesis was performed because of roentgenologic evidence of the presence of fluid. No penicillin was instilled. Hemophilus influenzae was cultured from this fluid. There was considerable drainage from the chest, which gradually decreased, and the lung continued to expand. The drain was removed on the forty-second postoperative day. Intramuscular administration of penicillin was discontinued on the twenty-sixth day in the hospital. Sulfadiazine was given from the twenty-eighth to the forty-first day in the hospital. Supportive therapy included administration of plasma and whole blood intravenously. The patient was discharged from the hospital on the sixty-first day.

Follow-up studies showed a greatly thickened pleura on the left side but no other abnormalities. Four months after discharge from the hospital the patient

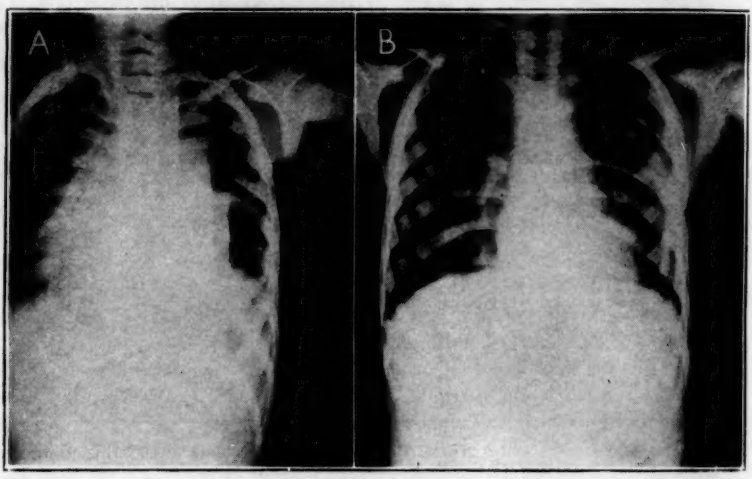


Fig. 3 (case 7).—*A*, roentgenogram of the chest made on the patient's admission to the hospital with the child lying on her right side, showing pneumothorax and several fluid levels on the left side; *B*, roentgenogram of the chest made on the patient's readmission to the hospital with acute bronchitis, showing the left lung to be normal.

had a recurrence of pain in the chest and fever. She was readmitted with a condition diagnosed as acute bronchitis, which responded well to penicillin therapy. A roentgenogram of the chest at this time showed the left lung to be normal (fig. 3*B*). No complications developed, and she was discharged on the fifth day from the hospital. Except for the scar of the incision, there was no thoracic deformity.

CASE 8.—W. R., a 4½ year old white boy, was admitted to the hospital on March 23, 1946. He had had a cough for ten days, dyspnea for six days, emesis for five days and diarrhea for three days prior to admission. His condition had been diagnosed as pneumonia by the family physician and had been treated with sulfadiazine. The treatment had resulted only in slight temporary remission of symptoms.

At the time of admission to the hospital, he had a temperature of 104 F.; respirations were 32 per minute, the pulse rate was 120 per minute, and he was dyspneic and cyanotic. Examination of the chest disclosed dulness to percussion, suppressed breath sounds and decreased tactile fremitus over the left side of the chest. A roentgenogram showed the entire left pulmonary field to be homogeneously opaque. A thoracentesis was done and 190 cc. of purulent fluid was recovered. A culture yielded Staph. aureus. Treatment was started with penicillin, 20,000 units given intramuscularly every three hours, and sulfadiazine sodium, given subcutaneously every eight hours. After the first thoracentesis there was complete collapse of the left lung and, despite repeated aspirations, the lung did not reexpand. A bronchopleural fistula was believed to be present.

During the next twelve days the patient received eight thoracenteses, and after each an average of 30,000 units of penicillin was injected into the pleural cavity. Cultures of the fluid yielded no organisms after the fourth thoracentesis. During this period the child had a continuous fever and was dyspneic, and the course of his illness steadily downhill.

On the thirteenth day in the hospital a rib resection was performed on the left side by Dr. Pat R. Imes. A large amount of thick purulent material was aspirated from the thoracic cavity, as well as several fibrinous clots. A drain was put in place, and the incision sutured around the drain. Intramuscular administration of penicillin was started again on the third postoperative day and was continued for seven days. There was considerable drainage from the cavity for the next several days, but on the sixth postoperative day the lung was almost completely reexpanded. The temperature fell to normal on the fifth postoperative day, and the dyspnea disappeared. The drain was removed on the twentieth postoperative day, and the patient left the hospital thirteen days later. A very small empyema pocket was still present. He was followed as an outpatient for several months; except for a thickened pleura on the left side, he has remained perfectly well.

Case 9.—E. K., a 2 year old white boy, was admitted on April 26, 1946. A diagnosis of pneumonia had been made six weeks previously. Sulfadiazine therapy was given, but the child showed only temporary improvement. He continued to run a low grade fever and had anorexia and dyspnea. On admission to the hospital he had a temperature of 103 F. and was mildly cyanotic. He had bronchial breathing in the upper lobe of the right lung, depressed breath sounds in the middle and lower lobes of the right lung and a flat percussion note in the lower half of the right side of the chest. The roentgenogram of the chest revealed an area of homogeneous opacity in the right lung. A thoracentesis was performed, and 15 cc. of a thick green exudate was obtained. Fifty thousand units of penicillin was instilled into the pleural cavity. No growth was observed on culture of the fluid. He was given 20,000 units of penicillin intramuscularly every three hours. On each of three successive days a thoracentesis was done, and each time only a small amount of thick greenish fluid was removed. With each tap 50,000 units of penicillin was given intrapleurally. No organisms were obtained on culture from any of the fluid removed. Since no improvement in the child's condition resulted from this therapy, surgical consultation was obtained and open drainage was established by Dr. R. A. Griswold on the ninth day in the hospital. Two hundred cubic centimeters of thick exudate and fibrinous clots was removed. Culture of this material yielded no organisms.

The intramuscular administration of penicillin was continued for four days postoperatively. A slight amount of purulent fluid continued to drain for twenty days. The patient was discharged on the thirty-second day from the hospital. Follow-up studies revealed no recurrence of the empyema.

COMMENT

We have presented 9 cases of empyema in children treated with varying amounts of penicillin. The ages of the patients ranged from 5 weeks to 5 years. There were 6 boys and 3 girls. Three patients required surgical drainage after unsuccessful penicillin therapy. Six patients responded well to medication, and surgical intervention was not necessary. Staph. aureus was the causative agent of the empyema in 4 patients and Pneumococcus in 2 patients. No organisms could be cultured from the empyema fluid of 2 patients (cases 5 and 9). In 1 patient (case 7) H. influenzae was observed after surgical drainage, but this organism was not believed to have been the etiologic agent.

All but 3 patients (cases 4, 5 and 6) had received one of the sulfonamide drugs prior to admission to the hospital. Two patients (cases 4 and 6) received none of the sulfonamide compounds at any time, and 2 patients (cases 5 and 7) received this form of chemotherapy after use of penicillin was discontinued. One patient of the latter group (case 5) was given only a small amount of penicillin, and recovery was possibly due to the sulfadiazine. Only 1 patient (case 8) received penicillin and a sulfonamide compound concurrently. All the patients who had surgical drainage had received sulfonamide drugs before admission to the hospital, and 1 (case 7) received sulfadiazine after operation.

Summary of Results in Nine Cases of Empyema Treated with Penicillin

Case	Age	Pathogenesis	Organism	Penicillin Therapy: Duration of Intramuscular Injections, Days	Penicillin Therapy: Number of Intrapleural Injections	Operative Treatment	Bronchial Fistula	Results of Therapy
1	2 yr.	Pneumonia	Pneumococcus type I	8	6	None	None	Cure
2	2½ yr.	Abscess of lung	Staph. aureus	15	0	None	None	Cure
3	5 yr.	Pneumonia	Pneumococcus type V	9	5	None	None	Cure ?
4	5 wk.	Indefinite	Staph. aureus	20	2	None	None	Cure
5	3 yr.	Pneumonia	Unknown	2	1	None	None	Cure
6	6 mo.	Pneumonia	Staph. aureus	18	7	None	None	Cure
7	5 yr.	Abscess of lung	H. influenzae ?	26	5	Yes	Yes	Cure
8	4½ yr.	Pneumonia	Staph. aureus	20	8	Yes	Yes	Cure
9	2 yr.	Pneumonia	Unknown	13	4	Yes	None	Cure

It is of particular interest to note the small amount of penicillin given several of the first patients treated. That small doses may be adequate for infants is illustrated in case 4, in which the patient received penicillin alone in amounts of 2,500 units intramuscularly every three hours

and as two intrapleural injections of 10,000 units each. This patient recovered without surgical drainage. The last 4 patients received 15,000 or 20,000 units of penicillin intramuscularly every three hours and frequent intrapleural injections of 30,000 to 50,000 units in 10 cc. of isotonic solution of sodium chloride. All patients who responded to medical treatment did so within one week after penicillin was started. The number of thoracenteses required varied greatly with the individual patient. One patient (case 2) received no intrapleural injections of penicillin and responded to intramuscular injections. The majority of the patients received at least four intrathoracic instillations of penicillin and 1 patient (case 8) as many as eight. In no patient was the pleural cavity irrigated with the solution of sodium chloride. We realize that the dose of penicillin was smaller than that advocated by most investigators,[7] who recommend daily thoracenteses at first, with instillation of as much as 200,000 units of penicillin into the pleural cavity.

The 3 patients who did not respond without surgical drainage had complications which may have prevented successful penicillin therapy. Two of these patients (cases 7 and 8) had pneumothorax with bronchial fistula. The lung could not be reexpanded by aspiration. One of these patients (case 7) had large bands and clots of fibrin, which could not be removed through a needle. The third patient (case 9) also had fibrin clots, and the purulent fluid was too thick to aspirate. If irrigation with saline solution had been done, this patient would perhaps have responded. No tests of sensitivity to penicillin were made, and several of the organisms causing the infections could have been resistant to penicillin.

The number of days in the hospital was nearly twice as great for the surgically treated patients as it was for those treated nonsurgically, but it should be recalled that for the former patients a medical regimen was first tried.

Our results for children are similar to those reported for adults,[8] about one half to two thirds of whom can be cured without operation if the causative organism is susceptible to penicillin. In our small series the patients responded rapidly and no chronic empyema occurred.

SUMMARY

Six of 9 patients with thoracic empyema responded to treatment with aspiration and instillation of penicillin into the plueral cavity. Penicillin was also given intramuscularly.

The causes of failure to respond to therapy are discussed.

University of Louisville School of Medicine.

FALLACIES INHERENT IN THE PROBAND METHOD OF ANALYSIS OF HUMAN PEDIGREES FOR INHERITANCE OF RECESSIVE TRAITS

Two Methods of Correction of the Formula

MADGE T. MACKLIN, M.D.
AND
HENRY B. MANN, Ph.D.
COLUMBUS, OHIO

SOME years ago, one of us (M. T. M.) wrote an article [1] showing that the proband method of analysis, which was designed to test the theory that a trait was being inherited as a recessive character in human families, was incapable of giving the expected 25 per cent of recessive homozygotes unless the families with more than 1 affected child were counted as often as there were affected children in them, in which case the method became identical with Weinberg's so-called sibling method. The publication of several recent articles in the medical literature using the proband method has prompted us to bring up the matter again, and to show in what circumstances the proband method is capable of yielding the theoretic 25 per cent of affected children, or, rather, what corrections are necessary to make the method accurate. At the outset, we emphasize that we are not advocating the inclusion of either of the corrected methods among the methods to be used in analysis of human pedigrees; other methods which are easier of application are preferable.

PERCENTAGES OF AFFECTED MEMBERS IN HUMAN FAMILIES SHOWING A RECESSIVE TRAIT

When two normal persons mate both of whom are heterozygous for a recessive trait, the chances of any one of their children showing the recessive trait are, of course, 1 in 4. The truth of this genetic law has been proved again and again for plants and animals in which the parents selected for the experiment are known to be heterozygous before they have any offspring whatever. Most recessive traits studied in man are disease conditions, and affected children are oftener born of

From the Department of Zoology and Entomology (Dr. Macklin) and the Department of Mathematics (Dr. Mann), of Ohio State University.

1. Macklin, M. T.: Methods of Correcting Pedigree Data, J. Hered. 29: 295 (Aug.) 1938.

normal heterozygous parents than they are of affected parents. The carrier condition, in which the person is heterozygous, is for the most part indistinguishable from the normal state, so that it is not known in human families that a parent is heterozygous until he produces affected children. Those matings of heterozygous persons which could be productive of affected offspring but chance to result only in normal offspring are indistinguishable in a population from any other mating of two normal persons which produces normal children. The group of normal children born of heterozygous parents is to be omitted from the total of the normal children, which are three times the number of affected offspring in the progeny of heterozygous parents. This omission of some normal children from the total inevitably raises the percentage of affected offspring in human families in which the parents are heterozygous for the defective trait. Thus, in any series of human families in which a recessive trait is being exhibited, the percentage of offspring affected will almost always be greater than the theoretic 25 per cent. The degree to which the observed percentage exceeds 25 depends on several factors. First, there is a variable degree of difference in the size of the families in the series studied. The smaller the family, the more widely does the observed percentage of affected children differ from the theoretic 25 per cent. Hence, if the series of families contained a large percentage with 2 or 3 children, the final percentage of affected offspring would be inordinately high. If the series was composed of many families with 12 or more children, the observed percentage of affected children would be much nearer the expected value of 25.

Second, the degree of departure from the expected 25 per cent depends on the degree of selectivity exhibited in collecting the families of the series. If one is analyzing cases published in the literature because the trait in question may be too rare to provide a large enough series of personal cases, one is likely to find an undue number of families with more than 1 affected offspring giving a still wider departure from the expected 25 per cent. It is more likely that a family with 2 or more affected children will be recorded in the literature than that a family in which there was only 1 child affected will be so recorded.

THE PROBAND METHOD

To overcome the error introduced by this excess percentage of affected offspring in human families with recessive traits, various methods of treating the data were devised. One such method was designated the proband method. It consisted in deducting from the total children in the family who were affected that group who represented the initial cases which brought the family to the attention of the observer. The remaining normal and affected children in the family

were then considered as the group in which one should find the 25 per cent of affected offspring. The basis of the theory appeared to be plausible, namely, that every child in the family had a 1 in 4 chance of being affected. If, therefore, one omitted the initial affected child, one should find among the remainder a close approximation to the theoretic expectations of normal and affected children. This reasoning seemed sound, but when one applied the method, not only to observed families in which a supposed recessive trait was appearing, but also to a group of theoretic families in which one had the correct number of families actually showing a recessive trait, the percentage of the affected offspring was far too low. It was only when the families were selected because they had more than 1 affected child, or when the families were all very large (thus limiting the number available for analysis), that an approach to 25 per cent was obtained.

A brief consideration of how recessive traits might appear in families of different sizes will make the reason for this difficulty clear, and, further, will show beyond doubt that the proband method, in which the initial cases are removed from consideration in the analysis, cannot give the theoretic percentage of affected offspring. Remembering that all families in which the parents were heterozygous but chanced not to have affected children are omitted from our studies, inasmuch as we are dealing only with families in which the offspring exhibit a trait, one can see that of 1 child families 100 per cent will be affected. In 2 child families, either 50 or 100 per cent will be affected, and the final percentage observed will depend on the ratio of the families that have both children affected to those that have only 1 child affected. Can it be predicted what that final ratio should be in families with 2 children, 1 or both of whom may be affected by a recessive trait? It can be, and the method is simple. Just as the operation of the law of probability gave the ratio of 3 normal children to 1 affected child in heterozygous matings, so the same law may show in how many families of 2 children both, and in how many only 1, should be affected. If the event of an affected child's being born is designated as a, and the event of a child being born normal, as $3n$, the ratios of families in which both children are affected, or 1 child or none is affected, will be given by expansion of the expression

$$(a + 3n)^s$$

where s is the size of the sibship. Therefore, in 2 child families, the expanded expression is

$$a^2 + 6an + 9n^2$$

In this formula, a^2 represents a family of 2 children both of whom are affected; $6an$, 6 families with 1 normal and 1 affected child, and $9n^2$, 9 families with both children normal. These 9 families are not included

in the study, since they have no affected offspring. Thus, the population with which one deals is composed of the families a^2 and $6an$; and if they occur as would be expected, in a random distribution, they are in the ratio of 6 families with only 1 child affected to 1 family with both children affected. In every 7 families of 2 children in whom the trait occurs, then, there is a total of 14 children (7×2); of these 14 children, 8 show the defect (6 from the 6 families with only 1 affected child and 2 from the 1 family with both children affected). The percentage of affected offspring in 2 child families is, therefore, 57.1.

For 3 child families, the procedure is the same. The expression $(a + 3n)$ is expanded to the third power, yielding

$$a^3 + 9a^2n + 27an^2 + 27n^3.$$

One family with all 3 children affected will be expected to every 9 families with 2 affected children and 1 normal child and to every 27 families with 1 affected child and 2 normal children. Again, one cannot include in the population being studied the 27 families with all 3 childen normal. There is a total of 37 families with some affected offspring, with a total of 111 children. Of these children, 48 are affected, made up of $3 + 18 + 27$ ($a^3 + 9a^2 + 27a$). The percentage of affected children in 3 child families is, therefore, 43.2. This is still much higher than the expected 25 per cent, but it is much closer to it than the 57.1 per cent found in 2 child families. Therefore, the larger the sibship, the more nearly does the percentage of affected children approximate the expected 25 per cent.

TABLE 1.—*Proband Method Applied to Theoretic Families of Two and Three Children Each* *

Size of Sibships	First Affected Sib	Other Affected Sibs	Normal Sibs	Percentage of Sibs Affected
2 (aa)	a	a	0	
(6an)	6a	0	6n	
Total	7a	a	6n	14.2
3 aaa	a	2a	0	
9aan	9a	9a	9n	
27ann	27a	0	54n	
Total	37a	11a	63n	14.8

* These families are placed in the ratios in which they would be expected to occur on the basis of random distribution. Exclusion of the first affected child in each family leaves a disproportionately large number of normal children, thus reducing the percentage of affected offspring to well below the expected 25. It is obvious that such a method cannot be expected to give 25 per cent of affected offspring in the families in which the range of numbers of children is that usually found in human families.

Knowing just how many families with varying numbers of affected children should occur theoretically, one may apply the proband method. The results are set out in table 1. Families of a larger number of children could have been included. It would have been evident that as

the size of the sibship increased the percentage of children affected as calculated by the proband method would also increase, although falling far short of the expected 25 per cent, even when families of 12 children are included. Small wonder, then, that in most instances in which the method is used the percentage of affected offspring is well below the theoretic expectation. The method permits of counting some families more than once if the family has been brought to the attention of the observer independently by more than 1 child and this helps to raise the percentage of affected offspring, since it is obvious that those families with the greatest number of affected children are the ones that can be counted the greatest number of times. If one were to group the families in table 1 as they are usually done in an analysis by the proband method, they would appear as follows:

Number of Families	Initial Affected Sib	Other Affected Sibs	Normal Sibs	Percentage Affected
44	44	12	69	14.8

As an illustration from the literature on the use of the method, the recent article by Penrose [2] dealing with phenylketonuria may be cited. In his study, 203 initial cases were considered, which were usually from institutions for the feebleminded. When the families were investigated, an additional 129 affected persons were found. There were also 509 normal sibs. Thus, the ratio of affected to normal children in the families, after the exclusion of the initial, or proband, cases, was 1:4. Penrose made the error of stating that this was 25 per cent, whereas the desired genetic ratio is 1:3, not 1:4. Therefore not 25, but 20, per cent of the remaining children were affected in the families cited by Penrose.

MEANS OF CORRECTION OF THE PROBAND METHOD

We have shown on theoretic grounds, and illustrated our point with a series of cases found in the literature, that the proband method is incorrect. Although this has been pointed out before, the method continues to be used, and authors still strive to make their findings fit into the expected percentage of 25. The proband method could be used if two things were recognized: (1) that one cannot arrive at the theoretic 25 per cent with its use and (2) that the percentage obtained with it differs for each size of sibship. Therefore, to make its use valid, one should first separate the families of a series into the various sized sibships, instead of grouping them all together, as is usually done. Second, one should test the observed percentages for each size of sibship against what one expects on theoretic grounds. Thus, in 2 child families, after having excluded the first affected child in each family, one should find

2. Penrose, L. S.: Phenylketonuria, Lancet 1:949 (June 29) 1946.

14.2 per cent of the remaining sibs affected. In 3 child families, after excluding the first affected child, one should find 14.8 per cent affected. In 4 child families, the percentage of affected children obtained by the rational use of this method would be 15.4, and in 5 child families, 15.9. This method, however, is no better than the others which do not exclude the affected child, but which accept it as a fact that 25 per cent of recessive homozygotes is not expected to appear in human families and which deal only with what is expected. But if one insists on using the proband method, one must use it correctly, either as just explained or, if one wants to approximate 25 per cent, by the use of a method now to be elucidated. The method involves a knowledge of the birth order in the family of at least the first affected child.

If the children up to and including the first affected child are excluded from analysis of the family, one will expect to find 25 per cent of the remaining sibs affected. This involves knowing the birth order of the first affected child, in order to know how many normal sibs are also to be excluded. Thus, if the first affected child in a family of 3 is the first child and the last 2 children are normal, the family is counted as one with 2 normal children. If the first affected child is the second child, with the third sib normal, the family is counted as one with 1 normal child; if the first affected child is the last child of a family, such a family drops out of the record. A disadvantage of the method is that one loses a certain number of families from the analysis by dropping out those in which the only affected child is the last of the family.

In table 2, data on families showing random distribution of 2, 3 and 4 children are set forth. In this table one sees not only the random distribution of families with 1, 2, 3 or more affected sibs but also that of affected children within the family. Thus, of the 2 child families, there are 6 families expected with 1 affected and 1 normal child to every family with both children affected. But the affected child can occupy one of two places in the family, first or second, and each position is equally likely. Therefore, 3 families will be expressed by *an*, with the affected child first, and 3 families by *na*, with the affected child second. In the 1 family with 2 affected sibs (*aa*), exclusion of the first affected child leaves *a* children. In the 3 *an* families 3 normal children are left; but in the 3 *na* families none is left after exclusion of the first affected child. The total number left is 4 children, with 3 normal sibs and 1 affected sib; the ideal ratio of 3:1. By the uncorrected proband method all 6 normal children were counted, with the result that the ratio of normal to affected children was 6:1. The analysis is given for 3 and 4 child families to show that one always obtains 25 per cent of affected children when all the children up to and including the first affected sib are excluded and the remainder of the family is considered in the ratio

of normal to affected children. This, of course, holds only when the families occur in the ideal ratios, with 1 or more affected, and when the distribution of affected members within the families is also completely ideal. In observed families, the percentage of affected children will depart from 25 to some extent, but if the trait shows random distribution the departure from the expected percentage will not be great. It should be pointed out that the same results will be obtained if all the

TABLE 2.—*Corrected Proband Method*

s *	ns †	nsc ‡	a §	n ‖	Percentage of Affected Offspring ¶
2.....	aa	a	1	0	
	3an	3n	0	3	
	3na	0	0	0	
Total.....		4	1a	3n	25
3.....	aaa	2a	2a	0	
	3aan	3an	3a	3n	
	3ana	3na	3a	3n	
	3naa	3a	3a	0	
	9ann	9nn	0	18n	
	9nan	9n	0	9n	
	9nna	0	0	0	
Total.....		44	11a	33n	25
4.....	aaaa	3a	3a	0	
	3aaan	3aan	6a	3n	
	3aana	3ana	6a	3n	
	3anaa	3naa	6a	3n	
	3naaa	3aa	6a	0	
	9aann	9ann	9a	18n	
	9nnaa	9a	9a	0	
	9naan	9an	9a	9n	
	9anna	9nna	9a	18n	
	9anan	9nan	9a	18n	
	9nana	9na	9a	9n	
	27annn	27nnn	0	81n	
	27nann	27nn	0	54n	
	27nnan	27n	0	27n	
	27nnna	0	0	0	
Total.....		324	81a	243n	25

* s is the size of the sibship.

† ns is the number of sibships expected in a random sample of heterozygous matings showing at least 1 child homozygous for the recessive gene. The birth order is also shown as it would appear if the affected offspring were showing random distribution within the families.

‡ nsc is the number and size of the sibships after removal of all children before and including the first affected child.

§ a is the number of affected children observed in nsc.

‖ n is the number of normal children observed in nsc.

¶ In every size of sibship the percentage of affected offspring obtained with this method is 25 when the affected sibs are showing random distribution throughout all the sibships.

children up to and including the second or the third affected child are excluded and the remaining normal and affected sibs are examined for the ratio of 3 normal to 1 affected. The objection again arises that such a procedure decreases the size of the group to be examined and offers

no advantages over the method of excluding only children up to and including the first affected.

Another disadvantage of this correction is, of course, that it introduces a second variable into the analysis, namely, that of departure from complete random distribution of affected children within the families. Although one expects the affected child to be either first or second half of the time in 2 child families, this is an ideal which is approached, but not necessarily reached, in any series of 2 child families. The same is true of the place in the family of the affected child in families of all sizes. With this method, any departure from the theoretic distribution of the birth order of the affected child would alter the percentage. This lowers the efficiency of the test.

COMPARISON OF THE PROBAND METHOD AND THE PROPOSED CORRECTIONS AS USED ON HUMAN DATA

Up to this point we have discussed the use of the proband method and the proposed corrections on theoretic populations in which the distribution of affected children in the various sized sibships showed complete random distribution. This ideal distribution is by no means always present in human families. We shall now apply these methods to a body of data[3] from human families in which congenital deafness appeared and in which the trait was assumed to be hereditary because other sibships in the pedigree had also shown its presence. Comparison of the results obtained with the various methods is shown in table 3. In a series of 58 families there was a total of 90 deaf children and 195 offspring with normal hearing. Deduction of the initial 58 affected children from these families left 32 other deaf children and 195 sibs with normal hearing. According to the proband method, the percentage of deaf persons was 14.1. If one tests the hypotheses that deafness was a recessive trait in these families and that the method should give a percentage of deafness of 25, one derives a value for chi-square (χ^2) of 14.7. This means that one can safely reject the idea that the actual percentage was really 25, and that deafness in these families was dependent on a recessive factor. But we have just shown that the proband method will not give 25 per cent even when used with families known to exhibit the recessive trait. Is the failure to give 25 per cent occasioned by the limitations of the method or by the fact that the trait of deafness is not a recessive one?

---

3. Macklin, M. T.: Studies on the Inheritance of Deafness in the Pupils of the Clarke School for the Deaf at Northampton, Massachusetts: II. Genetic Analysis of the Pedigree Data of the Clarke School Pupils, Laryngoscope **56**:583 (Oct.) 1946.

To answer this, we may apply other methods which we know should give good results if the trait is a recessive one. The correction as suggested by one of us (H. B. M.) was applied; and knowing the birth order of the children in these families, we were able to exclude all the normal sibs occurring before the first affected child, as well as the child with the initial case of deafness. With this correction, only 113 normal sibs were left, and the percentage of deaf sibs was 22.1. The value for χ^2 was 0.58, and we should expect as much deviation from 25 per cent as we now obtain in about 40 per cent of such series.

TABLE 3.—*Comparison of Proband Method and Proposed Corrections as Applied to Human Pedigrees*

First Deaf Sibs	Other Deaf Sibs	Normal Sibs	Percentage Affected	X^2
	Proband Method of Analysis			
58	32	195	14.1	14.7
	Mann Method			
58	32	113	22.1	0.58

Proband Method Corrected for Sibship Size (Macklin Method)

No. in Family	No. of Families	First Affected Sibs	Normal Sibs	Other Affected Sibs	Number of Expected Affected Sibs	Percentage of Expected Affected Sibs
2	12	12	10	2	1.70	14.2
3	8	8	12	4	2.37	14.8
4	7	7	18	3	3.23	15.4
5	10	10	33	7	6.36	15.9
6	5	5	22	3	4.12	16.5
7	9	9	47	7	9.12	16.9
8	2	2	14	0	2.43	17.4
9	3	3	20	4	3.56	17.8
10	0	0	0	0	0.00	18.3
11	1	1	9	1	1.87	18.7
12	1	1	10	1	2.09	19.1
Total	58	58	195	32	36.85	16.2

The expected and observed values agree closely when the necessary corrections based on correct reasoning are applied. This shows that the method as ordinarily used is worthless.

Hogben's Formula

Observed Number of Deaf Sibs	Expected Number of Deaf Sibs		
90	95.73	$\sigma = 5.95$	Diff. = 5.73

We then applied the second correction of the method, proposed by one of us (M. T. M.), in which the expected percentage of children affected was calculated for each sized sibship, as described earlier in the paper. The data are set forth in the third part of table 3. In the last column is placed the set of percentage values which the proband method actually should give, instead of the 25 per cent which Weinberg said should be obtained. Even for sibships as large as 12, only 19 per cent would be deaf if we excluded 1 deaf offspring from each family. In the next to the last column is given the number of deaf sibs which would be expected with this method when properly applied. It is to be

seen that 36.85 children, or only 16.2 per cent, were expected to be deaf, and 32 actually were. Thus, when the method is used correctly, it gives results which show that deafness is behaving as a unit recessive factor in these families.

Finally, the method which Hogben [4] used is summarized in the last part of table 3. The number of deaf persons in these various families expected on the basis of the Hogben formula is 95.73, and the observed number is 90 (32 + 58). The standard deviation is 5.95, which value is greater than the observed difference between the calculated and the observed values. From the values obtained with either of the two corrections of the proband method here proposed, or with the Hogben method, one would conclude that the trait of deafness is behaving as a recessive in these families, whereas the results obtained with the proband method as originally proposed would lead one definitely to discard such a hypothesis.

A second illustration from cases reported in the literature shows the inaccuracy of the proband method. The published cases of Jervis [5] on phenylketonuria did not give the place in the family of the affected children; hence, one of the corrections outlined previously cannot be applied. With the Hogben formula, however, the data can be tested. With the proband method, the percentage of affected persons in his series is 15.8, with a χ^2 of 6.5 if the condition is supposed to be recessive. This would lead one to discard the idea that phenylketonuria is dependent on a recessive gene. The Hogben formula gave a value of 60.85 for the calculated number of affected offspring, and the observed number was 59. One would now accept the idea that this trait is a recessive one.

A third illustration may be given. Andersen and Hodges [6] reported cases of the familial occurrence of fibrocystic disease of the pancreas, tested their observations by the proband method and arrived at 22.4 as the percentage affected. This value was derived either by counting some of the families twice, when 2 affected children were both patients of the clinic, or by including some families not listed in the table. If the families in the table are counted but once, there are 20 families, with 25 affected offspring and a total of 57 children. When the 20 children first affected are subtracted from the 57 children, a total of 37 children remains, of whom 5 were affected, yielding a percentage of 13.5 affected offspring. This is well below the 25 per cent expected and would lead one to reject the hypothesis that fibrocystic disease of the pancreas is a recessive trait. Utilization of the Hogben method on

4. Hogben, L. T.: Nature and Nurture, London, G. Allen & Unwin, Ltd., 1939.

5. Jervis, G. A.: Phenylpyruvic Oligophrenia, Arch. Neurol. & Psychiat. **38**: 944 (Nov.) 1937.

6. Andersen, D. H., and Hodges, R. G.: Genetics of Cystic Fibrosis of the Pancreas with a Consideration of Etiology, Am. J. Dis. Child. **76**:62 (July) 1946.

even these few families gives a calculated value for affected children of 25.69 per cent, while the observed value was 25 per cent. There is thus almost perfect agreement. Had Andersen and Hodges not had more than 1 of the children of a family as patients, so that each family was counted but once, they would have been led to a conclusion other than that which they accepted on the basis of 22.4 per cent, namely, that fibrocystic disease of the pancreas was a recessive trait.

It is to be hoped that workers who are analyzing human pedigrees for the presence of recessive traits will abandon the proband method, which cannot possibly give 25 per cent of affected offspring if the trait being analyzed is actually recessive, and if the families have not been selected because they have more than 1 affected child. At this point, we wish to make it clear that we are not proposing either of the methods of correction as desirable for analysis of human pedigrees. There are other methods available, such as the one proposed by Hogben, which are easier of application and which give reliable results. We merely emphasize the following points: 1. The proband method as now used is misleading. 2. If one insists on obtaining from heterozygous matings the ideal 25 per cent of affected offspring, a revision of the method is needed. This revision should consist in discarding not only the initially affected offspring, but also all the normal offspring who had been born in the family prior to the affected child. 3. If one insists on using the method as originally devised by excluding only the initially affected child, the families must be grouped according to their size, and each size of sibship must be analyzed for its deviation from the percentage expected for a sibship of that size. In table 3 these percentages are set forth for families up to 12 children. Standard deviations have not been worked out because they have already been presented for Hogben's method in his tables.

SUMMARY

It is evident from theoretic considerations that the proband method of analysis of human pedigrees for inheritance of recessive traits by exclusion of the initial affected offspring and estimation of the percentage of those affected among the remaining sibs cannot give the theoretic 25 per cent when the trait in question is known to be a recessive one and the families have not been particularly selected because they had more than 1 child affected.

A method of correction is explained which permits of close approximations to 25 per cent if the trait is a recessive one and if the families in the series show random distribution. This method is not recommended, since it introduces a variable, in addition to the deviation from the expected ratio of families with 1, 2 or more affected offspring in the various sized sibships, namely, the deviation from the expected distribu-

tion of affected persons within the family. Moreover, it does not utilize all the available information. The method has been explained merely to correct a false application of the proband analysis as practiced by investigators.

A second series of corrections described in the paper may be used. Families are to be divided into groups on the basis of the size of the sibship, and each group is analyzed separately; the percentage of affected persons in each sibship is not even a close approximation to 25; also, the percentage differs for each size of sibship. The expected percentages of affected sibs for families up to 12 children are given. The method used by Hogben offers an easy, accurate method of analysis and should supplant the proband method, even when accurately applied by means of the aforementioned corrections.

Case Reports

STREPTOMYCIN TREATMENT OF EMPYEMA CAUSED BY HEMOPHILUS INFLUENZAE

A. J. FISHER, M.D., and E. B. SHAW, M.D.
SAN FRANCISCO

THE LITERATURE abounds in references to cases of empyema, with particular emphasis on technics of treatment. Burpee[1] reviewed a series of 500 cases in 1936, while Hochberg and Kramer[2] reported on 300 cases and Lanman and Heyl[3] analyzed a large series, both in 1939. Shanks,[4] in 1944, compiled an excellent review of the literature and an analysis of 169 cases in Dayton, Ohio, since 1927. Most authors are in agreement that pneumococci account for 75 to 80 per cent of all cases of empyema, with streptococci and staphylococci etiologically involved in all other cases except for approximately 1 per cent, in which rare pleural invaders, such as Escherichia coli, Brucella abortis, Ascaris lumbricoides and Hemophilus influenzae, are implicated. The object of this paper is to present in detail the history, hospital course and subsequent follow-up observations in a case of empyema caused by H. influenzae in which treatment was with intramuscular and intrapleural administration of streptomycin. A careful review of the literature did not reveal any similar case except for the one reported in July 1946 by Ory, Jackson and Finland,[5] in which the empyema was due to a gram-negative organism and was cured with penicillin, and statistical reference to 5 cases of influenzal empyema recently reported by the National Research Council, with Dr. Chester S. Keefer as chairman[6]; the nature of the latter report, however, prohibits a detailed review.

REPORT OF A CASE

J. A., an American white girl, 10 years of age, was admitted to Children's Hospital, San Francisco, on March 12, 1946, after an illness which dated from February 14, at which time she experienced an infection of the respiratory tract

1. Burpee, C. M.: Acute Empyema in Infants and Children: Statistical Study, Arch. Pediat. **53**:449-462 (July) 1936.

2. Hochberg, L. A., and Kramer, B.: Acute Empyema of Chest: Review of Three Hundred Cases, Am. J. Dis. Child. **57**:1310-1337 (June) 1939.

3. Lanman, T. H., and Heyl, H. L.: Empyema in Children, New England J. Med. **221**:1003-1009 (Dec. 28) 1939.

4. Shanks, P. J.: Empyema of the Lung: Review of Literature and Analysis of One Hundred and Sixty-Nine Cases, Am. J. Surg. **66**:224-244 (Nov.) 1944.

5. Ory, E. H.; Jackson, G. G., and Finland, M.: Empyema Cured by Intrapleural Penicillin, J. A. M. A. **131**:1035-1039 (July 27) 1946.

6. Keefer, C. S.: Streptomycin in Infections, report of the Council on Pharmacy and Chemistry, J. A. M. A. **132**:4-11 (Sept. 7) 1946.

involving the throat and upper bronchial passages. She recovered quickly from this infection and was quite well until February 26, when she complained of generalized weakness and headache and seemed feverish. Two days later, on awaking, she was unable to talk. Her muscular weakness seemed to increase. She was taken to Shasta County Hospital, where her condition was diagnosed as pneumonia and she was treated with penicillin and a sulfonamide drug. While in the hospital she was delirious and continued to be aphasic. After ten days of treatment at Shasta County Hospital, she was transferred to Children's Hospital with the suspected diagnosis of poliomyelitis, based on the generalized weakness of her muscles, accompanied by aphasia.

Physical examination at the time of admission revealed that the child was acutely ill, with a temperature of 102 F., a pulse of 155 and a respiratory rate of 60 per minute. She was severely dyspneic and had a pronounced expiratory grunt. Physical signs were limited mainly to the thorax. The percussion note was dull posteriorly on the right side from the angle of the scapula down; breath sounds were diminished, and many coarse rales interspersed with fine ones were audible over this area. A few fine rales were also heard at the base of the left lung. The heart was dilated, its sounds were of poor quality, a gallop rhythm was present, but no murmurs were audible. The abdomen was somewhat distended. There was a peculiar brawny edema of the ankles and feet, as well as over the sacrum. There were partial paralysis of the right side of the face and definite aphasia, although the child understood questions well and would nod the answers. A diagnosis of lobar pneumonia in the right lung with possible empyema and cerebral abscess or embolism was made at this time. The cardiac enlargement was thought to be accounted for by intoxication.

Laboratory data obtained at the time of admission revealed a hemoglobin content of 68 per cent and a white blood cell count of 14,800, with 87 per cent polymorphonuclear leukocytes. A specimen of urine showed a heavy cloud of albumin and 10 to 15 red blood cells and 5 to 7 white blood cells per high power field. The spinal fluid was normal. The child was placed in an oxygen tent and given penicillin, 30,000 units, every three hours.

During the next three or four days in the hospital the edema over the sacral region, ankles and feet increased. The heart continued to gallop, with the apex impulse in the anterior axillary line. A specimen of urine showed an increase in red blood cells, from 10 to 15 to many per high power field. The possibility of rheumatic pneumonitis and carditis was considered, and treatment with acetylsalicylic acid, 10 grains (0.65 Gm.) every four hours, was started. After this therapy, the temperature dropped to normal and stayed at that level until the first week in April. By March 20 all rales had disappeared from the chest, although the breath sounds continued to be diminished. The percussion note was dull over the base of the right lung below the angle of the scapula. The facial weakness and the aphasia had practically subsided. The urine continued to be loaded with red blood cells. Because of a drop in the hemoglobin content to 48 per cent by March 21, the patient was given two blood transfusions, one on March 22 and the other on March 24, resulting in a rise in the hemoglobin content to 70 per cent. The blood pressure on March 28 was 148 systolic and 100 diastolic, and chemical studies of the blood on March 30 showed 60.3 mg. of nonprotein nitrogen and 8.2 Gm. of protein, with 3.14 Gm. of albumin and 4.6 Gm. of globulin per hundred cubic centimeters. On March 29 all medication was stopped and the patient remained afebrile for approximately one week. She continued to pass large quantities of blood in the urine. A Mantoux test on April 3 gave a negative reaction

Results of Chemical Studies of Blood, Urine and Empyema Fluid

	Blood							Urine				Empyema Fluid		
Date, 1946	Hemoglobin, Gm./100 Cc.	Erythrocytes, Millions	Leukocytes, Thousands	Polymorphonuclear Leukocytes, %	Lymphocytes, %	Eosinophils, %	Sedimentation Rate (Linzenmeier)	Color	Albumin, Reaction	Red Cells *	White Cells *	Leukocyte on Smear	H. influenzae on Smear	H. influenzae on Culture
March 12	9.8	3.3	14.8	87	12.5	...	10 min.	Brown	3+	10-15	5-7	.....	.....	.....
March 13	....	....	...	..	..	...	.....	Red	3+	Full	3-6	.....	.....	.....
March 23	Transfusion, 500 cc.							Brown	3+	Full	5-10	.....	.....	.....
March 25	10.1	3.32	...	..	..	...	.....	Brown	3+	Full	8-10	.....	.....	.....
April 1	8.7	2.7	8.2	82	13	2	.....	Red	2+	Full	...	.....	.....	.....
April 8	Transfusion, 450 cc.							.....	...	....	...	.....	.....	.....
April 9	10.1	....	...	..	..	...	.....	Red	2+	Full	...	.....	.....	.....
April 11	8.1	....	...	..	..	...	.....	Red	2+	Full	Few	Many	0	Many†
April 13	....	....	9.4	86	13	0.5	.....	.....	...	....	...	.....	.....	.....
April 18	8.7	2.9	9.7	78	18	4	.....	Brown	3+	Full	...	Full	Few	Many†
April 25	8.4	2.8	5.8	73	27	...	.....	Brown	3+	Full	4-6	Many	1-4	Many†
April 26	Transfusion, 500 cc.							.....	...	....	...	Mod.	4-10	Many†
May 2	....	....	...	..	..	...	.....	.....	...	....	...	Mod.	0.2	Few†
May 4	13.3	4.5	4.5	70	30	...	.....	.....	...	....	...	Few	Rare	Rare†
May 8	12.8	4.0	3.4	69	25	...	.....	Brown	3+	Many	...	Few	0	0†
May 13	10.1	....	4.1	61	38	...	.....	.....	...	....	...	.....	.....	.....
May 14	9.5	3.2	5.4	63	30	1	.....	Red	3+	Many	...	.....	.....	.....
May 20	9.3	3.2	5.4	35	60	1	.....	.....	...	....	...	.....	.....	.....
May 25	....	....	...	..	..	...	.....	Yellow	1+	Many	3-6	.....	.....	.....
May 27	9.0	3.0	4.4	52	46	2	15 min.	.....	...	....	...	.....	.....	.....
June 5	11.3	....	...	..	..	...	30 min.	Yellow	1+	Few	Rare	.....	.....	.....
June 29	12.8	4.4	7.5	63	36	2	40 min.	Yellow	±	Rare	0	.....	.....	.....
August 28	15.1	5.0	6.6	53	40	4	115 min.	Yellow	1+	0	0	.....	.....	.....

* Number per high power field. † During streptomycin therapy.

with a dilution of 1 : 1,000. On April 4 the spleen was felt for the first time 1 cm. (0.4 inch) below the left costal margin. A roentgenogram made on April 4 was read as showing the uncertain presence of air or of a gas-containing cavity in the upper portion of the lower lobe of the right lung, which was partially encapsulated along the posterior lateral wall of the chest. The appearance of the organ suggested empyema.

On April 8 the child was given another transfusion. After she had received approximately 180 cc., her temperature spiked to 105.4 F. and then continued to run a septic course. For the next week her temperature ranged from normal to 103.8 F. On April 13 a thoracentesis was performed, with the needle piercing the eighth interspace on the right side in the posterior axillary line. Three cubic centimeters of thick, purulent material and 5 cc. of air were recovered. From this pus a gram-negative, pleomorphic organism resembling H. influenzae both morphologically and culturally was grown initially and was recovered from succeeding taps. This organism did not show capsular swelling with either type A or B anti-Hemophilus-influenzae serum and was not further identified.

A roentgenogram made on April 15 showed an increase in the amount of fluid in the right pleural space since April 5. On April 17 a thoracentesis yielded 50 cc. of thick, brownish pus from the seventh intercostal space on the right side of the chest. The child was placed under penicillin therapy, 30,000 units every three hours, without appreciable change in the septic course of her illness during the next six days. In view of the nature of the organism recovered, it was decided to try streptomycin, which was secured through the cooperation of Dr. Keefer. A thoracentesis was performed on April 23 with removal of 40 cc. of thick, purulent material and the instillation into the pleural space of 100,000 units of streptomycin in 10 cc. of isotonic solution of sodium chloride. Intramuscular administration of streptomycin was also started, the dosage being 250,000 units every three hours. Thoracic taps were performed on April 24, 25, 26, 27 and 29 and on May 1, 2 and 4, during the course of which 500,000 units of streptomycin in 20 cc. of isotonic solution of sodium chloride was instilled into the pleural cavity after each aspiration of pus. It was noted that each succeeding thoracentesis yielded pus which was progressively thinner and which showed a decrease in the number of organisms on smear, from 10 to 15 per high power field in the initial specimen of pus to 1 to 2 per high power field in the last specimen. On April 26, the fever continuing, sulfadiazine, 0.5 Gm. every three hours, was administered along with the streptomycin.

During and after her course of intramuscular and intrapleural injections of streptomycin, from April 22 to May 13, the child had daily fever, with temperature peaks ranging from 101.4 to 104 F., but the cessation of streptomycin therapy on May 4 was followed by pronounced improvement in her symptomatic condition—she began to eat again, became more cheerful and ceased to complain of the pain in the chest which was so persistent during the intrapleural aspirations and injections. The urine gradually changed from dark brown, on May 8, to clear, on May 25, although microscopically still showing many red blood cells.

Thoracic signs also showed progressive clearing in the field of the right lung, as indicated both by a decrease in the area of impaired resonance below the right scapula posteriorly, with improved auscultation of breath sounds in this area, and by evidence from roentgenograms of the chest made on May 9 and 14, of progressive lessening in density of the fluid in the posterior inferior portion of the right side of the chest; it was no longer possible to distinguish a fluid level.

On May 13 the child's temperature rose to 104 F. at 4 p. m. A blood culture made at this time yielded no organisms, and the child seemed free of symptoms despite the hyperthermia. Surgical exploration was considered at this time to determine the possibility of an empyema cavity, walled off in the interlobar fissure. In view of the improvement in roentgenographic and physical signs, a short period of continued conservative therapy was agreed on. After the spike to 104 F., the daily elevations gradually decreased until the temperature leveled off at normal on May 23 and remained below 100 F. thereafter.

Meanwhile, the hemopoietic system showed toxic effects, with a drop in hemoglobin content from 92 per cent, on May 4, to 62 per cent, on May 27. The leukocyte count on all occasions was below 6,000, with a low of 3,400 and 69 per cent polymorphonuclear leukocytes on May 7 (just after completion of the sufadiazine-streptomycin therapy). The great drain of erythrocytes from the kidneys probably accounted in large measure for the precipitous drop in hemoglobin. By May 22 the child was sitting beside her bed in a chair, bouncing a ball about her cubicle and retrieving it scooter fashion on her chair. On May 25 she walked with assistance, and on May 28 she was discharged from the hospital. At the time of discharge, she was eating voraciously, appeared in high spirits and showed only a small area of persistent dulness and diminished breath sounds just below the right scapula posteriorly. Laboratory studies at the time of discharge revealed a hemoglobin content of 62 per cent, 3,060,000 erythrocytes and 4,400 leukocytes, with 52 per cent polymorphonuclear leukocytes, 46 per cent lymphocytes and 2 per cent basophils. The sedimentation rate (Linzenmeier technic) at this time was 18 mm. in fifteen minutes. A specimen of urine showed a trace of albumin and many red blood cells, 3 to 6 white blood cells per high power field and a rare granular cast.

The child reported to Children's Hospital for reexamination on June 5, 19 and 26. On these occasions, her physical signs showed progressive clearing, so that resonance over the right lung posteriorly on June 26 almost equaled that over the left side, with a similar improvement in the quality and volume of breath sounds. On this last visit, the gain in weight amounted to approximately 15 pounds (6.8 Kg.) over the weight at discharge and laboratory data also reflected her rapid convalescence. The hemoglobin was 12.8 Gm. per hundred cubic centimeters (88 per cent); the red blood cells numbered 4,400,000 and the leukocytes 7,500, with 63 per cent polymorphonuclear leukocytes and 36 per cent lymphocytes. The sedimentation rate at this time was 18 mm. in forty-two minutes. Fluoroscopic and roentgenographic examinations on June 26 showed a definite clearing of the inflammatory process previously present in the lower lobe of the right lung; there now remained only residual pleural thickening posteriorly and laterally, just above the costophrenic sulcus in an interlobar fissure. The remainder of the pulmonary fields was clear. The size of the heart was within normal limits, with slight relative predominance of the left auricle. The tip of the spleen was visible below the lateral costal margin, indicating moderate enlargement. We concluded from the roentgenographic examination that there was residual pleural thickening at the base of the right lung but that there were no indications of active infection.

J. A. returned to her family on July 5, in a condition differing considerably from that in which she left them. She continued under a regimen of abundant rest, limited activity and administration of supplementary vitamins and ferrous sulfate and revisited the hospital on August 28 for further check-up. At that time she appeared to be in robust health subjectively and objectively. Her

weight was 68 pounds (30.8 Kg.) and her blood pressure 98 systolic and 64 diastolic; physical signs of her illness were absent except for very slight impairment of resonance and breath sounds over the right lower pulmonary field posteriorly in a small area just below the angle of the scapula. The blood count appeared entirely normal: The hemoglobin measured 15.1 Gm. per hundred cubic centimeters (104 per cent); the red cell count was 5,060,000 and the white cell count 6,650, with 53 per cent polymorphonuclear leukocytes, 40 per cent lymphocytes and 4 per cent eosinophils. The urine showed a faint trace of albumin and was normal microscopically. The sedimentation rate (Linzenmeier method) was 18 mm. in one hour and fifty-five minutes. A roentgenogram of the chest was interpreted as showing a minimal amount of pleural thickening in the right costophrenic angle and laterally about the lower lobe of the right lung. The pulmonary fields were clear, and the heart and aortic arch were within normal limits.

The child is to continue her present convalescent routine and return for further check-up.

COMMENT

Patients are rarely encountered with such a multiplicity of symptoms—aphasia, weakness of the right side of the face, pneumonia, empyema, carditis and nephritis—attributable to a single organism. Blake [7] stated that such complications are possible; the appearance of the complete range in one case is, fortunately, a rarity.

The manifestations of involvement of the central nervous system are probably best explained on the basis of cerebral emboli—bacterial or thrombotic—rising at the site of the primary infection in the lungs. Similar embolic phenomena affecting the kidneys may also account for the urinary findings. The cardiac dilatation and arrhythmia must be attributed to myocardial damage from toxins of the invading organism, which seem also to have exerted a pronounced depressant action on the hemopoietic system.

The initial rapid clinical response of the infection to penicillin is notable—subsidence of fever within forty-eight hours after admission—but the organism soon became penicillin fast, as indicated by sensitivity tests four weeks after admission, with chick embryos utilized as culture medium. There was luxuriant growth of the organism in mediums containing 140 units of penicillin per cubic centimeter. Growth of the same organism was inhibited by 14 units of streptomycin per cubic centimeter; accordingly, massive doses of this drug were administered to the patient both intrapleurally and intramuscularly (chart). As the aspirated material from the last thoracic tap failed to yield any organisms, no tests for increased resistance to streptomycin could be conducted.

From the standpoint of painful reactions, injections of streptomycin were much less well tolerated than those of penicillin by this patient, who received large doses of each drug. The injections of streptomycin appeared highly painful at the intramuscular site of administration and seemed to cause continuous pain in the right pleural cavity; however, the pain in both areas subsided immediately after cessation of intragluteal and intrathoracic administration of the drug. Another peculiar

7. Blake, F. G.: Influenza, in Cecil, R. L.: A Text-Book of Medicine, ed. 3. Philadelphia, W. B. Saunders Company, 1933, p. 6.

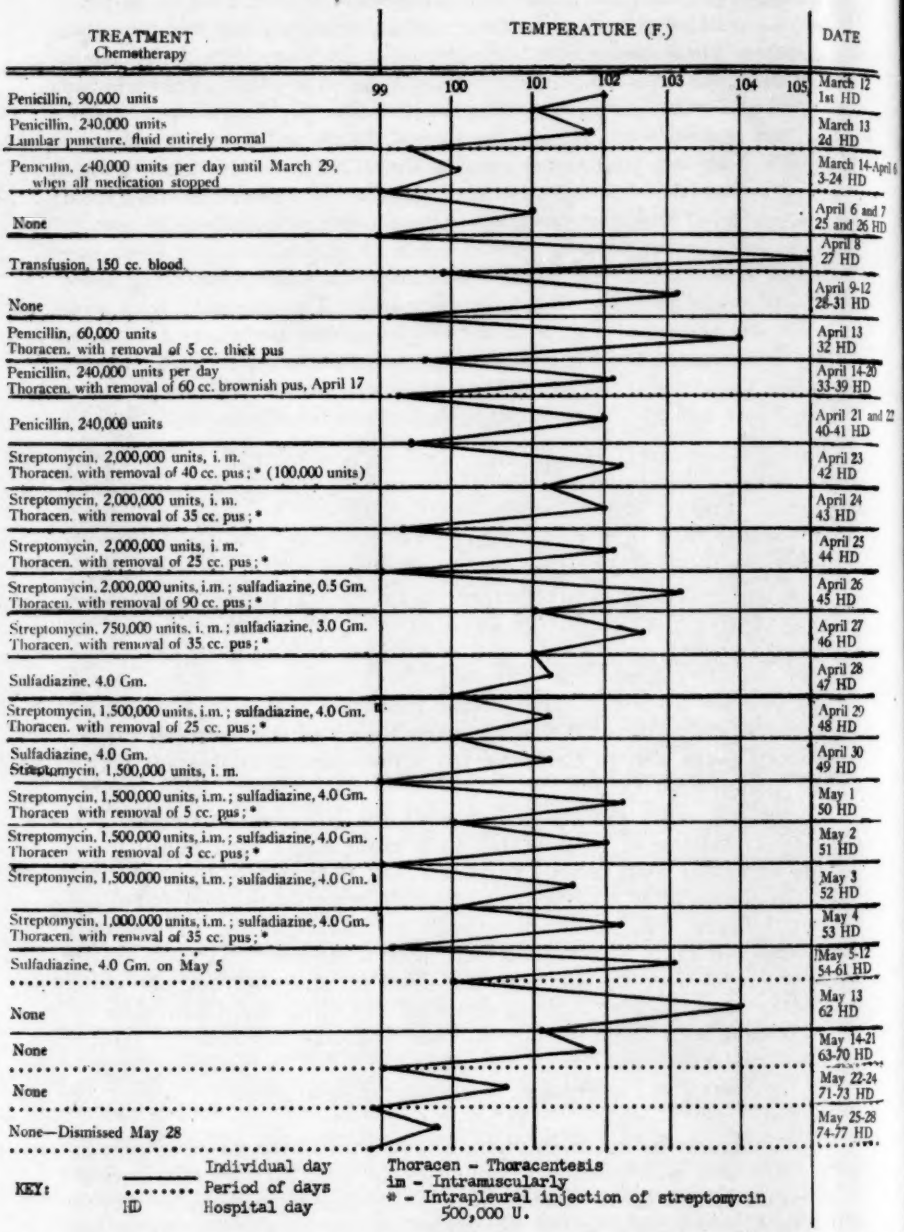


Chart showing temperature and treatment during days in the hospital.

observation in this case was the failure of the patient's septic course to change throughout the ten day period of streptomycin therapy, as indicated on the chart. Symptomatically, she continued to be acutely ill and refused almost all food, vomited frequently and appeared listless. On cessation of streptomycin therapy, these symptoms cleared rapidly, despite a continued febrile course with temperature spikes to 104 F. for the following week and up to 102 F. for the week thereafter. Subjectively, she seemed completely cured and was confined to bed only under severe protest, despite the septic temperature.

Follow-up examinations of the child have been highly gratifying, as indicated in the table. The examination of August 28 revealed that the patient was practically well, with only mild pleural thickening on the right side as a residual sign of her widespread infection. She looked as healthy and as vigorous as the thoracic signs and the laboratory data would indicate, and should soon be returning to school.

From the purely scientific viewpoint, it is unfortunate that therapy was not restricted to use of streptomycin as a single agent. Confronted, however, as we were, with an infection of desperate severity and with unexplored therapeutic possibilities, we can hardly regret, in retrospect, having experimented with all available agents. There seemed to be no avenue of approach to a prompt and indisputably specific cure. It is our conviction, based on careful observation, that streptomycin contributed most importantly to the successful outcome.

There are occasional cases of infection of the respiratory tract, such as this, in which results of bacteriologic studies are inconclusive, or have been altered by previous sulfonamide therapy. In such cases, untyped strains of H. influenzae may well be the etiologic agent and streptomycin the preferable therapeutic agent.

SUMMARY

The history, hospital course and follow-up observations in the case of a 10 year old girl with empyema caused by Hemophilus influenzae are detailed. The case is unusual because of the extrathoracic findings of aphasia, weakness of the right side of the face, cardiac enlargement, arrhythmia and nephritis present on her admission to the hospital.

After her entry all symptoms subsided on treatment with penicillin within two weeks, followed two weeks later by a return of the septic course, which was uninfluenced by penicillin. At this time, H. influenzae was isolated from the empyema cavity on the right side, and the organism was found sensitive to 15 units of streptomycin per cubic centimeter in cultures on chick embryos.

The empyema cavity was aspirated eight times, with a decreasing yield of organisms on smear with each succeeding tap. After each aspiration 500,000 units of streptomycin was injected into the cavity, while 250,000 units every three hours was simultaneously administered intramuscularly, for a total dose of 20 Gm.

After a protracted convalescence of three months, the child appears completely well with, as her only residual effect, slightly diminished resonance and breath sounds, attributable to a thickened pleura on the right side posteriorly.

TRANSPOSITION OF AORTA AND PULMONARY ARTERY

With Intact Interventricular Septum, Patent Foramen Ovale and Closed Ductus Arteriosus

BÉLA HALPERT, M.D., AND VERNON D. CUSHING, M.D.
OKLAHOMA CITY

IMPROVED methods in the diagnosis and treatment of congenital heart disease have revived interest in cardiac anomalies. Correct diagnosis requires a thorough knowledge of these anomalies and of the abnormal circulation resulting from them. A comparatively rare group of cardiac anomalies occurs with transposition of the great arterial trunks. The transposition is usually associated with interventricular septum defect, open foramen ovale and patent ductus arteriosus. It is also not unusual for the transposition to be associated with any two of the aforementioned communications. However, transposition of the arterial trunks with an open foramen ovale alone is exceedingly rare.

In a tabulation of 92 cases of transposition of the great arterial trunks, Kato [1] listed 9 such instances. He omitted the case of Owen and Kingsbury [2] and that of Moore [3] but added 1 of his own. The case here reported is an example of this type of anomaly, namely, complete transposition of the aorta and pulmonary artery with intact interventricular septum, patent foramen ovale and closed ductus arteriosus, and it brings the total of the recorded instances in the available literature to 13.

REPORT OF A CASE

J. M. D., a white boy 3 months of age, was admitted to the University of Oklahoma Hospitals, Sept. 24, 1945. The child was born June 16, at term. It was the mother's first pregnancy. Labor and delivery were uneventful. The child weighed 9 pounds (4,082 Gm.) and was blue. Cyanosis persisted and became exaggerated on crying. Except for the cyanosis, the child's development seemed unimpaired. On September 23, on two occasions, the infant became pale and the pulse weak and rapid. Examination on admission the next day showed that the child was well developed and fairly well nourished. There were pronounced cyanosis and a pinpoint rash over the face, neck, trunk and extremities, which did not fade on pressure. On percussion the heart was observed to be enlarged to the right and

From the Department of Pathology, the University of Oklahoma School of Medicine.

1. Kato, K.: Congenital Transposition of Cardiac Vessels: Clinical and Pathologic Study, Am. J. Dis. Child. **39**:363 (Feb.) 1930.

2. Owen, S. A., and Kingsbury, A. N.: The Diagnosis of Congenital Heart Disease in the Newborn, Including a Record of Cases of Foetal Endocarditis and Maldevelopment, Brit. J. Child. Dis. **21**:161, 1924.

3. Moore, R. A.: Transposition of the Great Arterial Trunks, J. Tech. Methods **12**:184, 1929.

to the left; the rate and rhythm were regular; a loud systolic murmur was heard over the entire precordium. Roentgenographic examination revealed that the shadow of the heart was globular and was increased to the left and to the right (fig. 1). The pulmonary fields were clear. The red blood cell count was 6,930,000; the hemoglobin content was 17 Gm. per hundred cubic centimeters; the white blood cell count was 18,900, with 41 per cent polymorphonuclear leukocytes, 42 per cent lymphocytes, 15 per cent monocytes and 2 per cent eosinophils. The urine was essentially normal. The patient was observed and treated symptomatically. The cyanosis persisted, and the child died suddenly on October 2, the eighth day after admission.

Necropsy was performed three hours after death. The child was 56 cm. in height and weighed 4,500 Gm. The skin was pale blue, with pronounced cyanosis of the fingers and toes. The left testis was at the internal opening of the inguinal canal. There were no anomalies of the abdominal organs. The blood vessels of

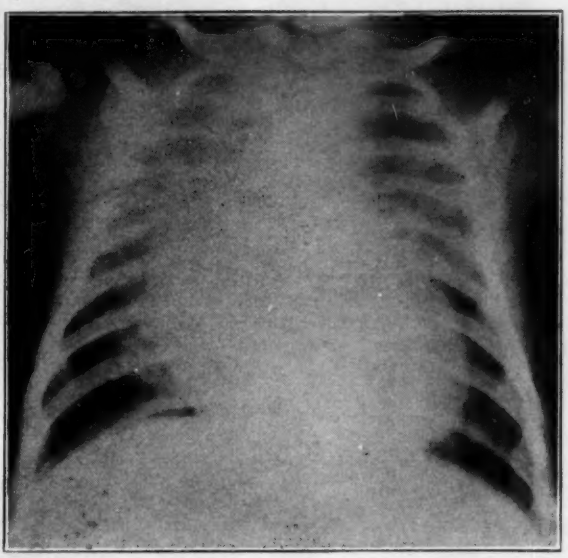


Fig. 1.—The roentgenographic shadow of the heart is globular and increased to the left and to the right.

the peritoneal surfaces were prominently distended. The liver reached 6 cm. below the right costal margin. There was no excess fluid in the peritoneal cavity or in the pleural cavities. The thymus was not enlarged.

The pericardial cavity contained 10 cc. of clear, straw-colored fluid. The transverse diameter of the heart was 9 cm., and that of the chest 11 cm. The heart measured 6 cm. from base to apex and 6 cm. across the base. The apex was rounded and made up almost equally of the two ventricles. There was complete transposition of the aorta and the pulmonary artery: The aorta arose from the right ventricle at the usual site of the pulmonary artery, and the pulmonary artery arose at the usual site of the aorta (fig. 2). The two vessels were of almost equal size. The ductus arteriosus was cordlike. There were no anomalies of the coronary sinus and its tributaries, or of the sites of termination of the superior vena cava, the inferior vena cava and the pulmonary veins. The azygos vein entered the

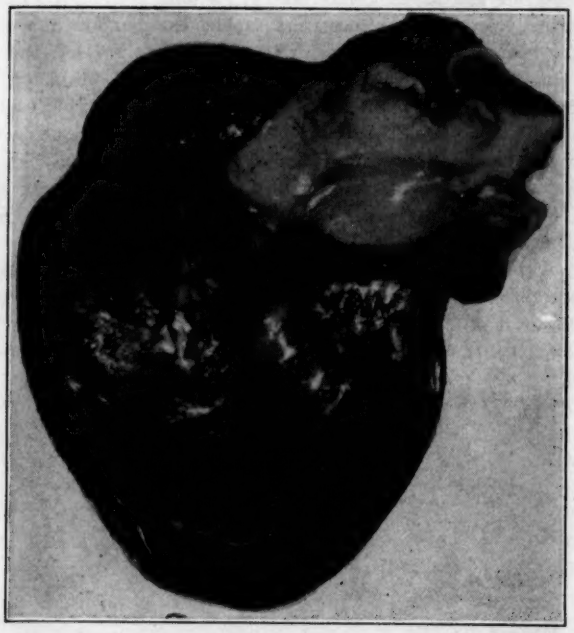


Fig. 2.—Complete transposition of the aorta and the pulmonary artery. The aorta arises from the right ventricle in place of the pulmonary artery; the pulmonary artery arises from the left ventricle in place of the aorta. The two are of almost equal size. The ductus arteriosus is cordlike.

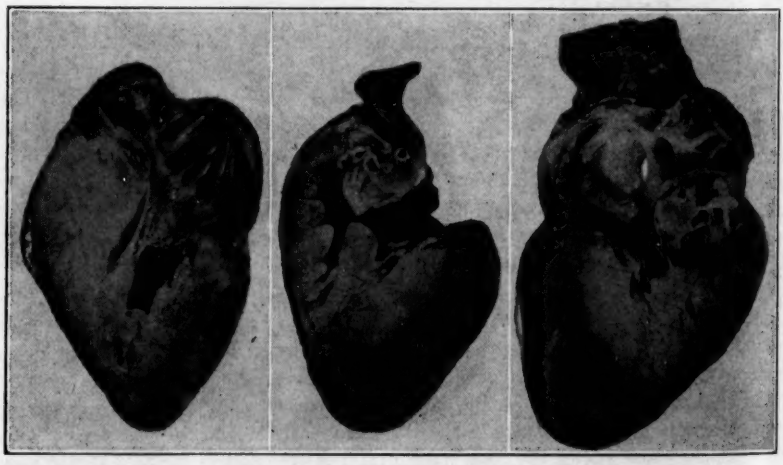


Fig. 3.—The right side of the heart opened, exposing the interatrial septum with the crescent-shaped foramen and the aortic orifice.

superior vena cava as usual, and there were no anomalies of the inferior vena cava or its tributaries. The right atrium was rather large. The foramen ovale was covered with a delicate membrane, with a crescent-shaped opening 0.8 by 0.3 cm. (fig. 3). The atrioventricular orifice was 3.5 cm. in circumference. The wall of the ventricle was 1.2 cm. thick. The aortic orifice was 2 cm. in circumference; its valves were delicate. The coronary arteries arose from the right and left aortic sinuses. Their course was as usual. The left atrium was normal. The atrioventricular orifice was 3 cm. in circumference. The wall of the left ventricle was 0.6 cm. thick. The interventricular septum was intact (fig. 4). The pulmonary orifice was 2 cm. in circumference. The ductus arteriosus was closed. The heart weighed 80 Gm.

Except for pronounced chronic passive congestion of the viscera and a slight focal lipid pneumonia, no other pertinent changes were noted in any of the organs examined.

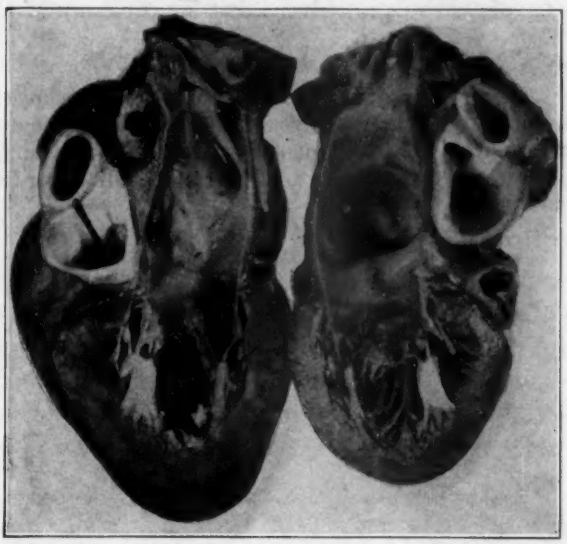


Fig. 4.—The left side of the heart opened, exposing the left atrium, the atrioventricular orifice and the ventricle. A probe is inserted into the pulmonary artery arising from the left ventricle. The interventricular septum is intact.

COMMENT

The anomaly here recorded is incompatible with life shortly after birth. Apparently, the complete transposition of the great arterial trunks was the only abnormality in this case. Although this anomaly resulted in an abnormal circulation, it did not interfere with normal intrauterine development. The oxygenated blood from the placenta reached the right atrium as usual. From here the blood which passed into the right ventricle was dispensed through the aorta into the systemic circulation. The blood which passed into the left atrium through the foramen ovale reached the aorta via the left ventricle, the pulmonary artery and the ductus arteriosus.

After birth the oxygenated blood from the lungs reached the left atrium. Here, through the patent foramen ovale it mixed with the venous blood of the right atrium. The blood entering the right ventricle passed through the aorta into the systemic circulation and was returned through the great venous trunks into the right atrium. The blood entering the left ventricle passed through the pulmonary artery into the lungs and was returned by way of the pulmonary veins into the left atrium. While the ductus arteriosus was still open, some blood probably could have passed between the aorta and the pulmonary artery in either direction. However, the importance of this communication seems to have been minimal, since at necropsy the ductus arteriosus appeared to have been closed for some time. Life, apparently, depended on the admixture of some oxygenated blood from the left atrium with venous blood in the right atrium through the foramen ovale. As the foramen gradually closed, the amount of oxygenated blood reaching the systemic circulation was so reduced that life could not be maintained.

SUMMARY

The case of a rare cardiac anomaly, complete transposition of the aorta and pulmonary artery with intact interventricular septum, patent foramen ovale and closed ductus arteriosus, in a boy 3 months of age is reported. This case is believed to be the thirteenth recorded instance of such an anomaly.

University Hospitals.

PNEUMOCOCCIC MENINGITIS

Recovery of An Infant Twenty-Five Days of Age Treated with Sulfadiazine and Penicillin

SIDNEY Q. COHLAN, M.D.
NEW YORK
AND
NATHANIEL H. SOLOMON, M.D.
FOREST HILLS, N. Y.

IN THE era preceding introduction of the sulfonamide drugs the mortality rate of pneumococcic meningitis was almost 100 per cent.[1] With the advent of these antibacterial drugs, numerous cases of recovery from this type of meningitis have been reported. Thus, with the use of the sulfonamide drugs, the mortality rate had dropped to levels varying from 33[2] to 66 per cent.[3]

Recently, even more favorable results have been reported in the treatment of pneumococcic meningitis with the combined administration of penicillin and sulfadiazine. Waring and Smith[4] observed only 1 death among 13 patients; Hutchins and Davies[5] reported 4 deaths among 14 children, and Smith, Duthie and Cairns[6] had 9 deaths among 38 patients treated with sulfadiazine and penicillin.

In spite of the sharp drop in the mortality rate following the advent of chemotherapy, the occurrence of this disease in infants under 3 months of age continues to present a serious problem. The high mortality rate and the frequent occurrence of complications in early infancy may be attributed to several factors, among which are: (1) difficulty of diag-

---

From the Service of Dr. Philip Cohen, Beth Israel Hospital, New York.

1. Goldstein, H., and Goldstein, H. Z.: Pneumococcus Meningitis: Report of Twenty Cases and Review of the Literature, Internat. Clin. **3**:155 (Sept.) 1927.

2. Steele, C. W., and Gottlieb, J.: Treatment of Pneumococcic Meningitis with Sulfanilamide and Sulfapyridine: A Statistical Study of All Reported Cases, Arch. Int. Med. **68**:211 (Aug.) 1941.

3. Rhoads, P.; Hoyne, A.; Levin, B.; Horswell, R.; Reals, W., and Fox, W.: Treatment of Pneumococcus Meningitis, J. A. M. A. **115**:917 (Sept. 14) 1940. Neal, J.; Applebaum, E., and Jackson, H.: Sulfapyridine and Its Sodium Salt in Treatment of Meningitis Due to the Pneumococcus and the Hemophilus Influenzae, ibid. **115**:2055 (Dec. 14) 1940.

4. Waring, A. J., and Smith, M. H. D.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcus Meningitis, J. A. M. A. **126**: 418 (Oct. 14) 1944.

5. Hutchins, G., and Davies, J. A.: Penicillin Treatment of Pneumococcus Meningitis in Infants, J. Pediat. **27**:505 (Dec.) 1945.

6. Smith, H. V.; Duthie, E. S., and Cairns, A.: Chemotherapy of Pneumococcal Meningitis, Lancet **1**:185 (Feb. 9) 1946.

nosis and, therefore, delay in treatment [7]; (2) lack of antibody response to the pneumococcus in children of this age group,[8] and (3) extensive fibrinoplastic exudate, with consequent blocking of the subarachnoid space.[5]

We have recently had the opportunity to treat an infant 25 days of age who had pneumococcic meningitis, and, because of her complete recovery, we thought the case worthy of reporting.

REPORT OF A CASE

A 25 day old infant was admitted to the hospital with a history of fever (temperature, 104 F.), lethargy and anorexia of eighteen hours' duration. There was no history of convulsion.

Physical examination revealed a well developed infant with a malar flush, lying quietly in no characteristic attitude. The temperature was 103 F. There were slight dyspnea, moaning on expiration and a pronounced startle reaction to external stimuli. Examination of the heart, lungs and abdomen showed them to be normal. The pharynx was injected. Nuchal rigidity was equivocal. The Kernig and Brudzinski signs were normal. The anterior and posterior fontanels were bulging moderately. The knee jerks were exaggerated.

Laboratory Data.—A blood count revealed 11,500 white cells, with 38 per cent polymorphonuclear leukocytes, of which 22 per cent were stab forms. The urine was normal. A roentgenogram of the chest showed nothing abnormal. A culture of material from the throat yielded pneumococci. A culture from the nose resulted in no growth. Because of the bulging fontanels, lumbar puncture was performed three hours after her admission and revealed a cloudy spinal fluid under slightly increased pressure. There were 3,800 cells per cubic millimeter of spinal fluid, of which 90 per cent were polymorphonuclear leukocytes. The sugar measured 11 mg. and the protein 269 mg. per hundred cubic centimeters. Pneumococcus type II was identified by a direct Neufeld reaction and by culture. The same organism was grown from blood cultures.

Course and Treatment.—Because of the appearance of cloudy spinal fluid, 50,000 units of penicillin (5 cc. of a solution containing 10,000 units per cubic centimeter) was introduced intrathecally. Penicillin and sulfadiazine were given by the continuous intravenous method for three days. The total dose of penicillin for this period was 240,000 units, and that of sulfadiazine, 3 Gm. The levels of penicillin in the blood reached 0.25 unit per cubic centimeter, while those of sulfadiazine averaged 16.6 mg. per hundred cubic centimeters.

At the end of twenty-four hours the infant's general condition appeared unchanged. A small amount of cloudy spinal fluid was obtained by lumbar puncture. Culture of this fluid yielded no pathogens, although a small number of pneumococci were observed on direct smear. Penicillin, 20,000 units, was given

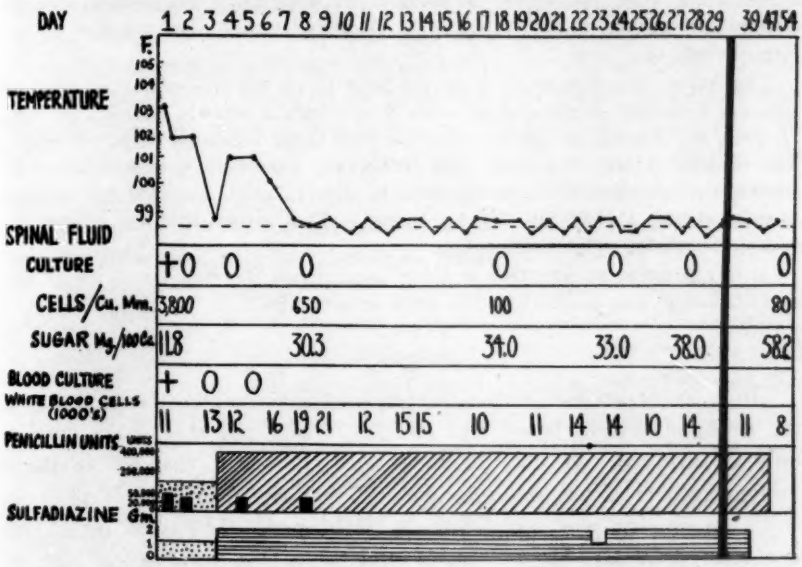
---

7. (*a*) Hartman, A. F.; Love, F. M.; Wolff, D., and Kendall, B.: Diagnosis and Management of Severe Infections in Infants and Children: A Review of Experiences Since the Introduction of Sulfonamide Therapy; IV. Pneumococcus Meningitis, J. Pediat. **27**:115 (Aug.) 1945. (*b*) Hogg, P., and Bradley, C. D.: Pneumococcus Meningitis in the Newborn, ibid. **26**:406 (April) 1945.

8. Davies, J. A. V.: Response of Infants to Inoculation with Type 1 Pneumococcus Carbohydrate, J. Immunol. **33**:1 (July) 1937.

intrathecally, and, as stated, the sulfadiazine and penicillin therapy was continued by the intravenous route. It is interesting to note that the pneumococci grown from the fluid obtained on the first lumbar puncture were observed to be extremely sensitive to penicillin, being inhibited in a dilution of 0.01 unit penicillin per cubic centimeter.

On the third day in the hospital the intravenous medication was stopped. Penicillin was then given intramuscularly in a dose of 400,000 units daily, and sulfadiazine was introduced orally in a dose of 1.2 Gm. daily. Only slight clinical improvement was noted. The fontanels continued to be full, and on that day the infant experienced a right-sided convulsion. We had planned to give penicillin daily by the intrathecal route but could not carry out this plan, because lumbar puncture resulted in a dry tap, presumably owing to a block in the subarachnoid space. An intraventricular puncture was attempted, without success.



Course of illness and effects of therapy in a case of pneumococcic meningitis in an infant aged 25 days.

Intramuscular administration of penicillin is indicated by the area of hachure; intrathecal administration, by solid black areas, and intravenous administration, by the dotted area.

Oral administration of sulfadiazine is indicated by horizontal lines, and intravenous injection, by the dotted area.

On the fourth day in the hospital there were definite signs of clinical improvement. The temperature dropped to 100.4 F. The infant now took her bottles well. The fontanels were less prominent, and there were no further convulsions. Spinal puncture was again unsuccessful, but on the following day a few cubic centimeters of blood-tinged spinal fluid was obtained. Penicillin, 20,000 units, was introduced intrathecally. No organisms were seen on smear, nor were any obtained on culture.

On the eighth day in the hospital clear spinal fluid was obtained for the first time. The cell count had fallen to 650 polymorphonuclear leukocytes per cubic millimeter. The sugar had risen to 30.3 mg. and the total protein had dropped

to 168.8 mg. per hundred cubic centimeters. Penicillin, 20,000 units, was injected intrathecally, and two hours later the infant had a generalized convulsion, lasting about one hour. This episode seemed to have been caused by the introduction of penicillin into the subarachnoid space.

Thereafter the infant's condition improved steadily. The temperature was normal on the eighth day. Full doses of penicillin and sulfadiazine were continued until the twenty-sixth day in the hospital, at which time the temperature had been normal for two weeks. The dose of sulfadiazine was reduced to 0.03 Gm. per pound (0.5 Kg.) of body weight, while penicillin was continued in the same dosage (50,000 units every three hours). The following day there were two episodes of convulsions, lasting two to three minutes each; and, although the spinal fluid at this time was clear, the dose of sulfadiazine was immediately restored to 0.12 Gm. per pound of body weight. There were no further convulsive episodes, and after two weeks of uneventful convalescence the sulfadiazine was discontinued on the thirty-ninth day in the hospital and the penicillin on the forty-seventh day.

The infant was discharged from the hospital on the fifty-sixth day with no apparent evidences of sequelae referable to the central nervous system. On Aug. 27, 1946, at 7 months of age, the child was seen in the follow-up clinic. Examination revealed a well nourished, well developed, apparently normal infant. An electroencephalogram taken at this time by Dr. John H. Taterka was reported as normal for a child of this age group. The parents refused consent for pneumoencephalographic examination.

It is interesting to note that in a five week period this infant received 35 Gm. of sulfadiazine and about 19,000,000 units of penicillin.

COMMENT

In a recent review of cases of pneumococcic meningitis occurring in the neonatal period, Hogg and Bradley [7b] reported that of 29 patients only 3 survived. It may be mentioned, however, that 2 [9] of the 3 infants recovered without therapy and that the diagnosis of pneumococcic meningitis was not definitely established. The third infant was one treated by Dr. Hogg himself, and there was no question that the etiologic agent was a pneumococcus. This infant was cured with the administration of sulfadiazine, and the case represents the first recovery from bacteriologically proved pneumococcic meningitis in the neonatal period. Our case is, to our knowledge, the second instance of recovery from pneumococcic meningitis in the newborn. The treatment in our case differed from that used by Dr. Hogg in that we used both penicillin and sulfadiazine. We employed both drugs, rather than sulfadiazine alone, because of the superior results reported in the literature from combined use of these drugs in the treatment of pneumococcic meningitis.[10]

9. Ravenil, S. F.: Spontaneous Recovery from Pneumococcus Meningitis: Report of Case in Newborn Infant, South. M. J. **29**:86 (Jan.) 1936. Uhr, J. S.: Pneumococcus Meningitis: Report of Case in Newborn Infant, Arch. Pediat. **47**:121 (Feb.) 1929.

10. Waring and Smith.[4] Hutchins and Davies.[5] Smith, Duthie and Cairns.[6]

There is little doubt that the recovery of our patient was due in a large measure to early diagnosis and, therefore, to prompt, intensive chemotherapy. Since penicillin is not excreted in significant amounts in the subarachnoid space when given parenterally,[11] it was necessary to employ penicillin intrathecally. The initial 50,000 units of penicillin introduced intrathecally resulted in a sterile culture of the spinal fluid twenty-four hours later. Though sometimes difficult, owing to subarachnoid block, Hutchins and Davies[5] suggested daily intrathecal administration of penicillin for an average of eleven days. The procedure is, however, not without danger. Optic nerve atrophy[4] and transverse myelopathy[12] have been attributed to it. However, Cairns and associates,[13] reporting on the results of penicillin treatment in British soldiers, noted that reactions to intrathecal administration of penicillin decreased with the increasing purity of the drug. In 1 of their cases in which there was a persistent reaction to intrathecal injection of penicillin, a purer preparation was found to be innocuous. Our patient had a generalized convulsion two hours after one of the intrathecal injections of the drug. Meningeal reactions are not necessarily a contraindication to the intrathecal administration of penicillin when one is confronted with a critically ill patient.

Pneumococcic meningitis is prone to relapses and recurrences. Among 67 cases of the disease, Applebaum and Nelson[14] reported 7 relapses. Sweet and associates,[15] in treating 16 patients, observed remissions in 3 of them, but when the dose of penicillin was reduced there was an immediate exacerbation of the meningitis. In the series reported by Smith, Duthie and Cairns[6] there were 12 relapses in 38 cases. This tendency to remission and recurrence raises the question of when to discontinue medication. Waring and Smith[4] continued use of penicillin for one week and sulfadiazine for two weeks after the temperature had returned to normal. In an infant who had several relapses, Sweet and associates[15] were compelled to continue therapy for one hundred and thirty-five days in order to effect recovery. Because of this tendency

11. Dumoff-Stanley, E.; Dowling, H. F., and Sweet, L. K.: Absorption into and Distribution of Penicillin in the Cerebrospinal Fluid, J. Clin. Investigation **25**:87 (Jan.) 1946.

12. Siegal, S.: Transverse Myelopathy Following Recovery from Pneumococcic Meningitis Treated with Penicillin Intrathecally, J. A. M. A. **129**:547 (Oct. 20) 1945.

13. Cairns, H.; Duthie, E. S.; Lewin, W. S., and Smith, H. V.: Pneumococcal Meningitis Treated with Penicillin, Lancet **1**:655 (May 20) 1944.

14. Applebaum, E., and Nelson, J.: Penicillin in Treatment of Pneumococcic Meningitis, J. A. M. A. **128**:778 (July 14) 1945.

15. Sweet, L. K.; Dumoff-Stanley, E.; Dowling, H. F., and Lepper, M. H.: Treatment of Pneumococcic Meningitis with Penicillin, J. A. M. A. **127**:263 (Feb. 3) 1945.

to recurrence, we decided to continue chemotherapy in our case until the temperature had been normal for about one month.

SUMMARY

A 25 day old infant recovered from pneumococcic meningitis after intensive combined therapy with penicillin and sulfadiazine. At 7 months of age follow-up study, including an electroencephalographic examination, revealed no evidence of postmeningitic sequelae.

NOTE.—The child was seen at 20 months of age, at which time examination revealed normal growth and development for this age. There was no evidence of sequelae referable to the central nervous system.

8 Gramercy Park (Dr. Cohlan).

62-65 Saunders Avenue (Dr. Solomon).

Progress in Pediatrics

NUTRITIONAL REQUIREMENT OF THE ADOLESCENT AND ITS RELATION TO THE DEVELOPMENT OF DISEASE

J. A. JOHNSTON, M.D.
DETROIT

IT HAS become almost a custom for the pediatrician to introduce the subject of adolescence with an apology to the internist for a seeming intrusion into his field. Yet, if the justification for the existence of pediatrics as a specialty rests at all on its concern with the problems of growth and development, there would seem little need for any attempt to defend his interest in this period. It will be evident from Dr. Stuart's discussion that the processes of growth in this period can be understood only by ignoring chronologic age and thinking in terms of physiologic age; a concept which involves ideally a continuous record of a person, the gradual acquiring of which may have taken twelve to fourteen years of a pediatrician's supervision. To interrupt such an experience abruptly at some arbitrarily chosen year may be to terminate the study at the very peak of a curve, when the rate of growth is changing. It will be stressed further that the attainment of sexual maturity and the termination of skeletal growth stand in direct relation to each other and that the time schedule which each follows is an individual one, with a wide range when measured in chronologic age. It follows from these observations that any attempt at limitation of supervision of the child to a particular period must be based on a measure other than time. Some such thinking will underlie my comments on metabolism, on nutritional requirements and on the relation of this age period to disease. Because considerations of growth rates, metabolism and food requirements are inseparable, some repetition of Dr. Stuart's material will be inevitable.

The implications of these two fundamental ideas, the individuality of the given patterns of growth and development and the comparatively wide range in the time of occurrence of these phenomena, were stated

From the Henry Ford Hospital.

This paper and the three which follow it were presented at the Panel on Adolescence at the meeting of the American Academy of Pediatrics, Hotel William Penn, Pittsburgh, Monday, Feb. 24, 1947.

1. Frank, L. K.: General Considerations: Certain Problems of Puberty and Adolescence, J. Pediat. **19**:294, 1941.

Submitted for publication May 20, 1947.

so clearly by Frank [1] that I can do no better than to quote directly from him.

> We cannot expect the individual boy and girl to meet these requirements [the tasks of life and the demands of maturation] effectively if in our various programs and practices in the home, in the school, the clinic and hospital, and in the youth organizations and elsewhere, we persistently deny the basic, ineradicable differences among individuals and impose upon them the tyranny of the norm. Perhaps in no other period except old age is there a greater need for the clinical approach which explicitly recognizes this individuality and mediates both the requirements and the needs of adolescents in accordance with the peculiar make-up and capacities of the individual boy and girl.

Robertson's [2] concept of adolesence as the final, S-shaped curve of growth, with a slight lag in the rate being followed by a sharp acceleration, and this, in turn, by a decelerative phase, terminating in cessation of growth, provides a good working background for a consideration of the period. His feeling that the process of deceleration might be associated with an increase in the incidence of disease can be substantiated by more examples than he gave. The increase in rate of growth, such as that in the prepuberty period, likewise carries its own hazards, which will be stressed when disorders of bone are considered.

BASAL METABOLISM AND DISTURBANCES OF THE THYROID GLAND

The smooth decline in the rate of oxidation from childhood to maturity is interrupted at this period, and there is a tendency for elevated rates to precede and for depressed rates to follow the period of maximum growth, which, in turn, is a reliable point of prediction of the sexual maturity which will follow shortly thereafter. In making determinations on a small number of girls at six day intervals for several months preceding and following the menarche, I have noted [3] a pronounced instability in the basal metabolic rate, with a tendency to a rhythmic rise and fall, high rates preceding and low rates following the onset of menstruation. Lewis and associates [4] reviewed a controversial literature on the point and recorded their own observations made over long periods, but at more widely separated intervals. They concluded that, while they could detect no absolute increase with age in the mean basal metabolism as referred to surface area, there was

---

2. Robertson, T. B.: The Chemical Basis of Growth and Senescence, Philadelphia, J. B. Lippincott Company, 1923.

3. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in the Growth Period: III. Puberty in the Normal Girl and in the Girl with Minimal Reinfection Tuberculosis, Am. J. Dis. Child. **59**:287 (Feb.) 1940.

4. Lewis, R. C.; Duval, A. M., and Iliff, A.: Effect of Adolescence on Basal Metabolism of Normal Children, Am. J. Dis. Child. **66**:396 (Oct.) 1943.

in both sexes a diminution in the rate of decrease in oxidation, which could be interpreted as a relative increase in metabolism. The fact that this period is marked by pronounced changes in the rate of growth would lead one to expect some such increase in metabolism. This instability would, in turn, favor an increase in the hyperthyroid states noted in the postpuberty period. At the Mayo Clinic 78 per cent of 157 cases [4a] of hyperthyroidism in children occurred between the ages of 10 and 14. Mild degrees of the condition were extremely common in the goiter belt before the widespread use of iodized salt, but the incidence has become much less. Mild hyperthyroidism should be borne in mind as a conditioning factor in the case of the high school child, whose scholastic and extracurricular schedules may require drastic modification. Much commoner is the occurrence of the hypothyroid state in the postpuberty years. Fatigue, pallor, a falling off in scholastic performance and menstrual irregularities are the commonest presenting complaints suggesting the presence of this condition. A slow pulse, low pulse pressure and subnormal temperature are additional factors calling for determination of the basal metabolic rate. The amount of thyroid required to correct the degree of hypothyroidism usually seen at this age is seldom more than ½ grain (0.03 Gm.). It should be recalled in this connection that if, in the period of growth the metabolism is elevated to too high a level, an interference in the storage of nitrogen and calcium similar to that associated with a depressed metabolic rate occurs, something which gives one pause in following the suggestion to give thyroid to the point of tolerance if this medication is not to be checked by determination of the basal metabolic rate.

CALCIUM AND NITROGEN METABOLISM

The metabolism of these two elements, which reflects the adequacy of the nutritional state more accurately than the weight, follows the curve of the rate of growth. The period of maximum growth in the girl, which in most cases precedes the onset of menstruation by about a year, is accompanied with high retentions of these two elements, whereas the decelerative phase of growth is characterized by their correspondingly low storage. It should be stressed that this decrease is a normal phenomenon and that with intake of these elements at a normal level the diminished ability to retain them produces no ill effect. There is not, however, during this unstable period the wide range of intake compatible with normal storage that occurs at the more stable periods of growth. It is my feeling that the diminished ability to retain these

4a. Kennedy, R. L. J.: The Thyroid Gland, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. I, chap. 38, p. 13.

substances, becoming more pronounced as the termination of growth is approached, may be an important factor in undermining nutrition and in conditioning unfavorably resistance to disease when the intake is marginal.

In regard to calcium, there is probably a wide range of intake compatible with adequate retention at most periods of growth, but in the adolescent period this would not seem to hold. Instances have been reported in which the difference between 1,100 and 1,300 mg. of calcium in the diet was the difference between a positive and a negative balance.[5] There is, likewise, a failure to appreciate the need of vitamin D during this period, although it is widely accepted that this need is conditioned as much by the rate of growth as by the intake of calcium and phosphorus. To the extent that the amount of retention with a given intake can be taken as a measure of optimum utilization, considerably more vitamin D would seem to be needed than is commonly given, and I would urge that 1,000 to 1,500 U. S. P. units per day be prescribed during adolescence. At the conclusion of growth I could measure no improvement after use of the vitamin. The amount of calcium I would suggest as optimal is 1.4 Gm., i. e., the amount (1.1 Gm.) contained in 1 quart (1 liter) of milk together with the other calcium-containing items listed in the accompanying tabulation.. When, for any reason a sufficient quantity cannot be given in these foods, the amount may be made up with basic dicalcium phosphate ($CaHPO_4.2H_2O$).

	Protein (Gm.)	Calcium (Gm.)
Milk, 1 qt.	28.8	1.15
Egg	6.0	0.03
Meat, fish or cheese, 2 large servings	46.0	0.32
Cereal, 1 serving, and bread, 3 servings	13.0	0.07
Dessert, containing milk and egg	3.5	0.10
Total	97.3	1.67

Vitamin D—1,000 U. S. P. units.

DISORDERS OF BONE

With changing rates in rapidity of growth, the situation would seem ideal for the development of skeletal disorders, and a number of these conditions are encountered—adolescent rickets, slipping of the upper femoral epiphysis and vertebral epiphysitis.

Follis and associates[6] described histologic evidence of rickets in the older child, of a degree which they felt may have no clinical significance.

5. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: VI. The Calcium and Vitamin D Requirements of the Older Child, Am. J. Dis. Child. **67**:265 (April) 1944.

6. Follis, R. H.; Jackson, D.; Eliot, M. M., and Park, E. A.: Prevalence of Rickets in Children Between Two and Fourteen Years of Age, Am. J. Dis. Child. **66**:1 (July) 1943.

I have studied an adolescent child referred to me for observation because vague aches and pains in the extremities led to the suspicion of rheumatic fever. Balance studies showed practically no storage of calcium until the patient received vitamin D. If there is any validity in the concept that the normal deposition of lime is the function of an equation

$$\frac{Ca \times P}{\text{rate of growth}} = K$$

then it is easy to visualize how frequently at this age this equation must be unbalanced by an alteration in the denominator.

Probably the most widely recognized disorder of bone associated with adolescence is the slipping of the upper femoral epiphysis. Its occurrence is sharply limited to the period corresponding with maximum growth in the two sexes, the average age being 12 years in the girl and 14 years in the boy. While there is as yet no general agreement on the cause of the disturbance, I have observed that the retention of calcium was low in a group of 5 children with this disorder and that in 3 of them the addition of vitamin D to the diet improved retention strikingly. In the other 2 children, administration of thyroid and testosterone further diminished retention. The low retentions of calcium that these children showed may have been referable to the fact that the studies were made during their convalescence from nailing of the epiphysis, but, unlike the adults, who showed poor retention after both rest in bed and fracture, these children did show immediate improvement in storage with the addition of vitamin D to the diet. As a group, children with this disorder are physically larger than their chronologic peers, and their size favors slipping in a joint weakened by inadequate mineralization. There would seem indicated in the management of a child with the body type susceptible to this condition a diet high in calcium and vitamin D and low in calories to limit gain in weight; with calories restricted intake of protein should be higher than usual, as discussed in the management of the obese child.

The type of vertebral epiphysitis seen at adolescence was described by King[7]; it occurs characteristically a few years later than does epiphysiolysis. Mild forms of it may represent the commonly observed "adolescent round back." Here, again, is a condition the occurrence of which is noted at the time of accelerated growth in the vertebral column, occurring after growth in the extremities has ceased.

OBESITY

This complaint is not basically a problem of adolescence; when it is possible to follow the growth of a child at frequent intervals, the tendency

7. King, E.: The Rarefying Conditions of Bone, Baltimore, Williams & Wilkins Company, 1935.

can usually be anticipated, but it can likewise be foretold that the tendency will become exaggerated during the adolescent spurt of growth. That it is not the result of hypothyroidism is now generally appreciated; Bruch [8] emphasized that such an explanation would be incompatible with the accelerated growth in height that most obese children show, the advanced bone age and the fact that the child is often advanced in mental age, though possibly retarded in emotional maturation. The reporting of a lowered basal metabolic rate is an error referable to the use of surface area standards for a type of body build in which the adipose tissue introduces an error into the calculation; reference to standards based on either height or excretion of creatinine brings out the true nature of the metabolic rate, which is actually slightly elevated

The management of the condition involves a diet high in protein and calcium and low in calories, as well as a sympathetic consideration of the psychologic factors that may be in the background. It is important that the morning meal contain protein; the diet I prescribe contains 1,400 calories, and of these, 20 per cent derive from protein. My difficulties in the handling of these obese children in practice have been referable as much to the parents as to the child.

TUBERCULOSIS

The factors at play during the decelerating phase of growth in adolescence would seem to bear a reciprocal relation to mortality from infection. Notably is this true in the case of tuberculosis; a sharp increase in mortality, corresponding to the differences in the time of attainment of sexual maturity, occurs at this period, first in the girl and later in the boy. That this increase represents an endogenous activation of a primary infection, rather than a reinfection from without, seems borne out by a follow-up study of over 1,000 reactors to the tuberculin test for varying periods up to twenty years.[9] In about 3 per cent of these reactors lesions of reinfection developed after their removal from contact and in a majority of this number, during adolescence. I have tried to sustain the thesis that anything which adversely affects the nutritional state becomes a factor in the development of the adult type of tuberculosis. Among such factors a prominent one is the diminished ability to retain nitrogen and calcium, which is characteristic of the phase of decelerating growth in the adolescent child. Practically, this observation means that particular attention should be paid to the maintenance of an optimal nutritional state in the child known to react to tuberculin. This care will involve not merely the provision of an adequate diet,

8. Bruch, H. B.: Obesity in Relation to Puberty, J. Pediat. **19**:365, 1941.

9. Johnston, J. A.; Howard, P. J., and Maroney, J.: A Quantitative Study of the Tuberculin Reaction in Childhood Tuberculosis, Am. Rev. Tuberc. **29**: 652, 1934.

but the seeking out of those factors which interfere with the utilization of nutrients—focal infection, departures from the normal metabolic rate or overexpenditure of energy. The child known to react to tuberculin should be examined roentgenographically at least once a year throughout adolescence, and oftener if intercurrent infection occurs.

MENSTRUAL PROBLEMS IN THE ADOLESCENT GIRL

My approach to the assessment and management of menstrual problems in the adolescent girl is made with three points in mind: 1. The range of time over which the first period may appear is wide—between the ages of 10 and 16, with a mean of 13. 2. The length of the cycle can be presumed to be irregular during the first two years, particularly common being an interval of about sixty days after the first period. 3. Anything which affects normal growth and development, whether it be diet, emotional difficulties, activity or the hormone state, will be reflected in an irregularity in the cycle. With these facts in mind, many complaints can be dismissed as not constituting "problems," but merely calling for an explanation of the usual course of events. When there is just reason for complaint, the following grouping of underlying causes has been useful in classifying the difficulties:

Nutrition.—Any departure from normal in the direction of either obesity or undernutrition may be reflected in a menstrual abnormality. Both conditions, in turn, may have their roots in a psychologic difficulty, the obese child using food as an escape mechanism from social maladjustment and the undernourished "teen-ager" losing appetite in her often futile attempt to carry on a school program beyond her capacity. An inadequate amount of protein in the diet has frequently been observed to be followed by amenorrhea, and it is at the moment an outstanding reason for the occurrence of this condition in the war-stricken areas.

Activity.—The combination of scholastic and social programs may make such demands on the adolescent's time that none remains for the normal amount of outdoor exercise so necessary for the achievement of optimal growth, and the inadequate exercise may, in turn, account for a menstrual difficulty. The effects on metabolism of curtailment of activity are too well known to justify withdrawal from gymnasium and swimming classes in an attempt to improve dysmenorrhea. A program of active gymnasium and outdoor exercise has actually been shown to shorten notably the time of painful menses, when contrasted with a plan which provided for rest during the menstrual period.

Glandular Dysfunction.—This aspect will be dealt with at greater length by Dr. Pratt. Of the hormonal influences which have a bearing on the menstrual difficulties of the several years that follow the onset of menstruation, by far the commonest is hypothyroidism. Fatigue,

pallor and secondary anemia are common accompaniments of a menstrual complaint. In a group which I studied, about one-third required thyroid, and of these, two-thirds were definitely benefited by it. The sensitivity of the person with a true thyroid deficit should be recalled; most of the children in this group needed as little as ¼ grain (0.016 Gm.); few required more than ½ grain (0.03 Gm.).

Consideration of these factors is not to deny the existence of a true organic basis for menstrual disorders; in 5 per cent of my patients gynecologic examination revealed an organic difficulty, and reference to the specialist in this field should not be too long delayed after the possibility of commoner causes has been eliminated. Too routine an employment of this direct approach is not, in my opinion, justified and has led to psychic trauma.

SUMMARY

Throughout this discussion, I have attempted to stress the individuality of the pattern of growth and its variability in terms of chronologic age, and, in turn, the effect of this on the child. It is regrettable that failure long before adolescence to appreciate the differences that distinguish one child from another result in classifying into school grades children who are of the same chronologic age but who differ from each other by several years in physiologic age and readiness for learning. When this failure becomes obvious at adolescence, the difficulties inherent in an attempt at regrouping would result in even greater problems.

I have made the point, too, that adolescence represents a phase characterized by changing rates in rapidity of growth and that there is implicit in this an added risk of pathologic development, most of which could be thought of in terms of basic nutritional elements, the provision of which might well be the largest contribution one could make to the child who so quickly will become the man.

2799 West Grand Boulevard.

PHYSICAL GROWTH DURING ADOLESCENCE

HAROLD C. STUART, M.D.
BOSTON

THERE ARE three major phases in the progress of growth from conception to full maturity. The first and the last of these phases are characterized by cycles of acceleration followed by deceleration in growth rates, both are accompanied with striking developmental changes. The middle phase, in contrast, is one of relatively steady, moderate progress in both growth and maturation. The term adolescence refers rather loosely to the last of these three major phases, to the time during which the child becomes a man or woman. The earliest and latest changes of this transformation take place insidiously and are not easily recognized or defined. They reach back well into what is usually thought of as childhood, or the stable middle period of growth, and they extend forward into what is, in most respects, adulthood. The major changes of adolescence, however, take place within a much shorter period and are recognized more readily. It is helpful to think of this middle period of adolescence as pubescence, separated from childhood proper by a preparatory or transitional stage, prepubescence, and from full maturity by a terminal stage, postpubescence. Pubescence may be defined by derivation as that period during which adult hair is developing in the pubic region. Technically, the period commences when hair first appears in this region and ends when the mature hair is fully developed. Practically, these events usually correspond with other more important ones, by which the period is recognized.

During prepubescence the rate of body growth begins to accelerate, the sex organs grow more rapidly and certain endocrine glands increase their activity. During postpubescence, growth in the major bony dimensions quickly comes to an end, but, in boys especially, the skeleton continues to gain adult robusticity through further local growth, as in the face, jaws and shoulders. Muscles also continue to increase in size and strength during this late period; here, again, the increase is far greater among boys than girls. Much of the growth of the sex organs takes place during the postpubescent years, after the person

From the Department of Maternal and Child Health, Harvard School of Public Health; the Department of Pediatrics, Harvard Medical School, and the Children's Hospital.

has attained approximate adult size and after he appears to have reached maturity in most other respects.

The early and late stages of adolescent development cannot be defined or delimited with any precision in terms of chronologic age because of the gradual transition from one stage to another and because of great individual variability in respect to age. Each stage may be thought of as lasting between two and three years in most persons, although from some points of view postpubescence lasts considerably longer. For example, a certain degree of physiologic sterility, probably dependent on lack of full sexual maturity, apparently persists from four to six years after the menarche.

Primary attention will be devoted in this discussion to the changes with growth which are characteristic of the period referred to as pubescence.

PUBESCENCE

Growth during pubescence is characterized by acceleration in the rate of increase up to a peak of rapid gain, followed, after a variable but, in the major body measurements, brief period of maximum growth, by rapid deceleration. This sequence of acceleration, maximum growth and deceleration characterizes the period, and it is recognizable in all human beings, as well as in the higher animals. It is reflected in most skeletal dimensions and, to some extent, involves all the body systems except the nervous and lymphatic systems. The brain, and hence the skull, have reached approximately adult size before pubescence, and the lymphatic structures atrophy to a considerable extent during this period.

The most profound changes associated with pubescence occur in the reproductive system, some of the sex organs increasing several times in size. Closely associated with this rapid growth of the sex organs are certain developments in the skin and other soft tissues, which are usually referred to as the secondary sex characters.

The duration of pubescence is variable, but is usually between two and three years. The accelerating phase of growth occupies the major portion of this period, but the first precipitous phase of deceleration is included as well.

The principal characteristics of the pubescent growth of the skeleton, including the muscles and the overlying soft tissues, may be listed briefly as follows:

1. The onset of pubescence is closely associated with a change from a fairly steady rate of growth in height to an accelerated one. Acceleration continues until maximum growth is attained, and deceleration sets in soon thereafter. The duration of this accelerated growth varies among persons and is hard to measure because the moments of change

cannot be recognized, but it is shorter for most persons than the curve for the average would suggest. When acceleration ends, deceleration takes place rapidly, and within a year in most instances the rate of gain has reached a slower pace than that before acceleration set in.

2. The rate of gain in most linear measurements follows the same sequence of acceleration, maximum growth and deceleration, all measurements reaching the peak at about the same time. However, they differ among themselves in the magnitude of these changes and in the duration of the several stages. By this means, proportional changes are brought about and sex differences are established, as, for example, in the breadth of shoulders and hips.

3. The period of accumulation of fat in the soft tissues characteristically coincides with that of the major growth of the skeleton, although the increase tends to commence during prepubescence and sometimes does not continue after rapid linear growth has set in.

4. The period of rapid growth of skeletal muscles is considerably longer than that of growth in height, particularly in the boy.

5. The rate of gain in weight, in contrast to that of gain in height, definitely increases each year both before and during prepubescence, so that the change in increment of weight at the onset of pubescence is less obvious than the change in that of height. It is usually recognizable only as a sharply accelerating change in the rate. Furthermore, owing to the increase of subcutaneous fat during prepubescence and the increase of muscle, as well as of certain bony dimensions during postpubescence, the curve of gain in weight tends to form a broader plateau at its maximum than does that of gain in height.

6. Maximum growth occurs most commonly in this country among girls during the thirteenth year of life and among boys during the fifteenth year.

With these general characteristics of the modal child in mind, it is important to remember that variability among persons is great during the period and to appreciate the principal ways in which variability manifests itself. The most significant variation is in the timing of the onset, peak and end of each phase of the pubescent cycle, that is, in the placement of the whole cycle in relation to chronologic age. If chronologic age is ignored, or is adjusted in relation to maximum growth or other landmark in the cycle, the whole pattern of change, or sequence of events, becomes much more uniform among persons. With this correction for variability in the timing of occurrences in pubescence, progress appears to be no less uniform and predictable than at other periods of growth. The variations in this timing in relation to chronologic age, however, are so great that one boy may have completed pubescence when he is the same age as another who shows

no sign of beginning it. Furthermore, an early maturing boy may reach maximum growth at an earlier age than a late maturing girl, even though girls on the average reach this stage about two years before boys.

There are several rather characteristic differences between persons of the same sex who reach maximum growth early and those who do so late. These differences suggest a high feminine component in early maturing persons of both sexes and a high masculine component in late maturing persons. Thus, early maturing children tend to have narrow shoulders, broad hips and short legs and to accumulate fat in the subcutaneous tissues readily, whereas late maturing children tend to show the reverse of this picture. Furthermore, early maturing persons tend to be large at onset of pubescence and to have large increments of growth over a relatively short period of maximum growth, in contrast to late maturing persons, who are small prior to the onset of pubescence and have smaller increments and a longer duration of maximum growth during pubescence.

Large size in childhood is in part due to advanced maturation, and, since this leads to a shortened period of growth, ultimate size is usually not so extreme as prepubescent size might lead one to anticipate. Obese children at this period are usually also large and advanced in general development. Their obesity is due to the tendency, previously mentioned, to store fat in the soft tissues, as a part of adolescent growth. This type of obesity must be distinguished, however, from the much less common form associated with retarded sexual development, particularly in boys, and with other signs of abnormal endocrine activities.

Growth of the reproductive organs and development of the secondary sex characters follow characteristic patterns of change in association with the major developments of pubescence. Accelerated growth of the primary sex organs begins before any of the secondary sex characters are discernible and is apparently well under way during prepubescence. As previously stated, these organs continue to grow and mature throughout postpubescence; in fact, the major growth of the uterus, and possibly of the testes, occurs during this period. Hence, maturation of these organs spans the long period of adolescence. The size of the testes may be noted in the examination of development, but the other primary sex organs are not so readily appraised. It is for this reason that the developmental stages of the secondary sex characters should be known and given attention.

Early changes in the areolas of the breasts are usually discernible in girls before any other changes are apparent, but rounding of the contours of the hips may be recognizable in some girls at about the same time. Although the papillae have been enlarging and the areolar areas broadening for some time, the first clearly recognizable change

in these regions is elevation of the areolas. This elevation is frequently noted in boys and somewhat later may become embarrassing to them. This first stage of breast development is usually referred to as the "bud stage." The next change involves enlargement and protrusion of the underlying breast in a conical eminence, from which the elevated areola still stands out. This stage is referred to both as the "primary breast" and as the "conical breast." Subsequent changes, dependent primarily on growth of glandular tissue, lead to enlargement and rounding out of the breast, with incorporation of the areola in the breast itself so that only the papilla protrudes. These changes lead to the "secondary breast," which is the mature breast prior to the first pregnancy. Much of the progress of the last stage takes place in postpubescence, the primary, or conical, breast being the stage usually atttained at the time of menarche.

The earliest appearance of the pubic hair at the base of the penis heralds the onset of pubescence in the boy and is the first secondary sex character to be noted. In a girl pubic hair appears about the labia majora shortly after the earliest change in the areolas of the breasts, and it spreads outward and upward, changing character as it becomes denser. The features of the development of the pubic hair deserving note are the area covered, the length of the hair, its coarseness, density and pigmentation and whether it is straight or curly. At the end of pubescence in both sexes it fills the triangle bordered above by the crest of the pubis and laterally by the creases formed by the thighs with the pubic folds. It has then become dense, long and curly and fully pigmented. In girls this is the characteristic picture at maturity, but in boys there is a variable amount of postpubescent extension upward toward, or even surrounding, the navel and outward onto the thighs. At the time of the menarche in girls pubic hair usually extends over most of the triangular area described, but it is still not fully developed in its other aspects.

Axillary hair usually appears several months after the pubic hair, and it progresses through most of the same changes. It is usually present, but is very immature, at the menarche. Shortly after the appearance of axillary hair facial hair in boys becomes apparent as a fine down on the upper lip. It extends in a characteristic manner to the chin and the sides of the face and becomes coarse, pigmented and dense. This character is well developed at the end of pubescence, but further changes take place throughout postpubescence. Adult hair begins to appear in the boy on other parts of the trunk and extremities late in pubescence, but its maturation is largely a postpubescent phenomenon. Although the vocal cords are developing male characteristics throughout the pubescence, change of voice in boys usually occurs at about the end of this period.

These changes in the reproductive system and in the tegumentary system are closely correlated in their timing with certain phases of pubescent growth. They are also correlated with corresponding stages of osseous development. There is a closer association between given stages of osseous development and the accompanying stages of physical growth and sexual maturation than between chronologic age and the latter. During pubescence, that is, after the secondary sex characters can be observed, the study of roentgenograms to determine the stage of maturation is of much less practical value than at earlier ages. This procedure is usually unnecessary after the secondary sex characters have begun to develop, because one can then recognize the stage of maturation which the child has reached and can predict with sufficient accuracy the age at which subsequent stages will be attained.

In using the stage of osseous development as a criterion for the degree of advancement, or retardation, in a child's maturation, study of

Differentiating Characteristics of Early and Late Pubescence

Early Pubescence	Late Pubescence
Large in late childhood	Small in late childhood
Body type feminine (broad hips, short legs)	Body type masculine (broad shoulders, long legs)
Maximum growth early	Maximum growth late
Growth rapid, over short period	Growth slow, over longer period
Ultimate Size Not as Extreme as in Late Childhood	
Menarche early in girls	Menarche late in girls
Early secondary sex characters	Late secondary sex characters
Osseous development earlier than average	Osseous development slower than average

a roentgenogram of the hand is the simplest and the most commonly used because several standards and methods of evaluation and rating of this area are available. A study of other regions of the body by experienced persons can add to the accuracy of the osseous age rating, but lack of adequate norms for these regions at present makes evaluation difficult.

It has been indicated that body growth, osseous maturation, growth of the sex organs and differentiation of secondary sex characters normally progress together in associated stages. As an example, girls who reach their maximum growth two years before the average will reach the menarche about two years in advance. They will also attain the successive stages of breast and hair development, will be advanced in osseous development and will also cease growing about this much in advance of the average. The accompanying table shows the common, or characteristic, differences between early and late maturing persons in these respects. Individual differences are frequently encountered, but the trend of association is an almost constant phenomenon. I am considering physical growth only, but it should be pointed out that

psychologic and emotional characteristics of adolescence appear in a somewhat parallel manner. Hence, the behavior at a given age of a late maturing girl may be expected to be very different from that of one who is maturing early.

Criteria for the appraisal of maturation during the adolescent years are of practical importance in connection with health examinations and, particularly, in the understanding of persons who manifest unusual behavior during this time. Recognition of advancement, or retardation, is necessary for sound advice regarding most health problems. The physician should learn to note the stages of development of the various sex characters which can be observed and to appreciate what hidden changes are probably associated with them. He may use increments of body measurements between examinations for this purpose also, provided that measurements have been recorded regularly so that changes in trends may be recognized. Studies of roentgenograms, hormone assays and determination of other physiologic changes may be used to advantage in unusual cases.

FACTORS INFLUENCING, OR ASSOCIATED WITH VARIABILITY IN ADOLESCENT MATURATION WHICH MAY HAVE SIGNIFICANCE FOR HEALTH

1. Food requirements are extremely high during pubescence. Fortunately, the appetite is usually voracious, so that enough suitable food will usually be eaten if it is made available. However, unsuitable foods will satisfy the appetite, and faulty habits of food selection formed in earlier years will often be carried over into this period and prevent the taking of an adequate diet. The principal need is for a high protein diet, covered by a liberal allowance of calories.

2. The obesity sometimes present during this period is important both from the physical and from the psychologic standpoint. The effect on participation in sports and other activities, and hence on muscular development, body mechanics and physical fitness at maturity, is probably great. The effects on social adjustments, the acquiring of skills and the child's emotional life are probably equally important.

3. Chronic undernutrition during childhood appears to retard development as well as growth. The onset and termination of pubescence appear to occur later among persons who subsist on poor diets than among those provided good and liberal diets. Racial differences in respect to age of pubescence seem to be explained in part by socioeconomic factors and national dietary customs.

4. Race, family and other hereditary factors, as well as climate, greatly influence the course of adolescence. A secular trend toward

an earlier attainment of adolescent development is clearly discernible in this country.

5. The regimen of rest and activity which are suitable for the prepubescent, the pubescent and the postpubescent child are obviously quite different. The fact that all three may be of the same age is probably of far less significance than that they are in different stages of development. The prepubescent child is fairly quiescent in respect to physical and physiologic change, for he is still a child. The pubescent child is in a stage of profound change and instability, often of physical stress and emotional turmoil. The postpubescent person is not yet a man, but he is growing much less rapidly and is far more mature, acquiring the last attributes of full maturity. These considerations greatly influence the need for and suitability of programs of training and physical education.

6. The rapid changes in growth processes during adolescence are known to have a profound influence on the course of tuberculosis and other diseases.

7. Developmental abnormalities in the endocrine or reproductive organs lead to many clinical problems during this period; but these, again, are outside the scope of the present paper.

8. Lack of uniformity in advancement, or retardation, in physical, intellectual or emotional fields gives rise to problems.

55 Shattuck Street.

IMPROVEMENT OF BODY MECHANICS IN ADOLESCENT CHILDREN

CLIFFORD D. SWEET, M.D.
OAKLAND, CALIF.

ONE OF the commonest problems presented to physicians by the adolescent patient is faulty posture or body mechanics. With the rapid growth in height that occurs in adolescence, all the earlier faults are made more apparent, even when they are not greatly increased in actual physical proportions. At this time, too, parents generally become much more aware of the physical appearance of their child than they were during his earlier years. This increased awareness of parents is based on many factors: the child's appearance in the more formal clothing demanded by his increasing social life; his greatly increased size, with the corresponding increase in any deformity which he may have; his lack of skill in managing his suddenly enlarged body and its members, and, most of all, their startled realization that the child can no longer be counted on to outgrow his undesirable physical traits and that these, in fact, have become "ingrown." All these factors generally cause parents to become increasingly critical of their child, with greater use of such nagging phrases as, "Stand up," "Sit up," "Throw your shoulders back" and "Flatten your abdomen," which not only arouse the child's antagonism but actually give him instructions that are without value.

The physician must instruct both the parents and the child in simple and effective means of improving body mechanics and must win the cooperation of the child by making a direct arrangement between himself and the child to carry out a program. First, the patient must be assured that he can accomplish results that are desirable without too great effort. Next, he must be helped to understand that his faults of posture and body mechanics are usual, unless he has some extraordinary deformity, and, therefore, are not a basis for personal criticism. All human beings follow a pattern of growth determined by natural forces, which can be modified and made more useful only by individual study and effort.

When standing erect with neither foot advanced, the human body has no single center of gravity but is overbalanced in the ventral direction. The upright position can be maintained only by muscular effort, by shifting the upper part of the body backward far enough to offset the force of forward rotation and by advancing one foot before the other

sufficiently to form a broad base on which balance can be maintained without muscular effort.

The static muscular effort which is demanded to hold the body fully upright (at its greatest height) can be maintained for only short periods, and relief from such fatigue is soon sought by allowing the body to fall into mutually balancing, superimposed opposing curves. This position throws the body into all the faulty alinements of the class C posture, that is, eversion and pronation of the feet, hyperextension of the knees, anterior tilting of the pelvis, prominent abdomen, increased lumbar lordosis, lowering of the shoulder girdle and forward thrust of the head. Since all skeletal muscle shortens to fit the limits of its use, any habitual posture soon becomes fixed within definite muscular limitations. While these shortened muscles can be stretched, they produce considerable discomfort when the customary stance is shifted sufficiently to bring tension on them or when an attempt is made to increase the range of motion about any joint. The young patient is quite correct when he says, "I am comfortable as I am and find any other way uncomfortable." He must then be assured that the discomfort will soon disappear and that the improved appearance and function of his body will repay his effort many times. Increase in running speed and skill in tennis or dancing, as well as the greatly decreased probability of sprains of the knee and ankle joint, can be safely promised any patient who will stretch the muscles that are too short. As he observes the fulfilment of the promise, his full cooperation is won.

The considerable number of patients who complain of backache, pains in the legs, painful feet and recurrent sprains must also be mentioned. The cooperation of such patients is easily gained, since with the relief of muscular strain pain is no longer present. Recurrent sprains of the ankle and knee joint can be cared for successfully only by thorough stretching of the calf and hamstring muscles, with concomitant strengthening of their opponents.

The hamstring muscles must be stretched and the calf muscles either stretched or developed if they are weak and too long. The gluteal muscles and all the muscles that contribute to the external rotation of the femurs and the quadriceps and the tibialis muscles must be strengthened and developed. The grasping power of the feet can be developed rapidly by walking barefoot on an inclined surface, to which the feet must cling in order to maintain balance. Increase in the grasping power of the feet automatically increases the strength of all the muscles which are brought into action by its use. Also, the importance of a lack of mechanical support from a short first metatarsal bone diminishes in

direct proportion to the development of the ground-gripping power of the feet and of their supporting muscles.

The hamstring muscles are effectively stretched by having the patient bend forward at the hips with the spinal column locked in full extension. In this exercise the weight of the trunk and head is brought to bear on the hamstring muscles as a stretching force acting about the hip joints as a fulcrum. The force should be applied gently at first and increased only as the muscles yield. If it is applied with sudden violence by raising the arms and throwing the body suddenly forward, the hamstring muscles may be injured or the lower part of the back seriously sprained. Kicking for height without flexing either knee, the spinal column or the opposite hip joint, and without ducking the head, is also an effective and easily learned method of stretching the hamstring muscles.

The quadriceps muscles are strengthened by having the patient lie on the back with one thigh fully flexed on the abdomen, the leg fully flexed on the thigh and the foot in full dorsiflexion while the other leg is held in full extension on the table. Without allowing the extended leg to flex, or the pelvis to rotate on the table, and with no plantar flexion of either foot, the patient extends the flexed leg as though a weight were being pushed vertically upward by the heel. When the limit of possible extension is reached, the leg is held forcibly in this position for a count of five, and then the heel is pushed forcibly against the periphery of its descending arc until it again rests on the table. This exercise stretches the hamstring muscles and strengthens the quadriceps by bringing both sets of muscles into strong opposing action throughout the maneuver.

The patient is taught also to stand with the spinal column fully extended, as though he were carrying a heavy load on his head. In fact, the most effective way to teach him to stand and to walk well is to have him carry a heavy sandbag on his head for a few minutes each day. This procedure is especially effective if, at the same time, he walks barefoot on an inclined plane. In some cases the muscles of the anterior portion of the shoulder girdle are so short and those of the posterior portion so weak that special exercises must be given to remedy the defect before the spine can be fully extended. Full extension of the spinal column is taught by having the patient drop the head as far back as possible in dorsal extension and then bring it up around the ears as an axis.

Finally, he is taught to stand with one foot before the other, resting his weight on both or on either, with his spine fully extended and both his knees and his hips slightly flexed. When he stands before a sink, a table or a workbench he is to place one foot well in front of the other,

while the knee and hip joints, being flexed forward, let him comfortably down to the level required by his work without strain on his back. In this position, when fatigue is felt, it is necessary only to interchange the positions of the feet for complete relief. This method of standing often brings relief from backache to the pregnant woman and to the mother in the months after delivery, when the care of her child demands much standing at sinks and tables, with lifting of the child many times each day. Incidentally, its adoption is helpful to the surgeon as well, when he must work at the operating table for long periods.

2940 Summit Street.

ENDOCRINE ASPECTS OF ADOLESCENCE

J. P. PRATT, M.D.
DETROIT

ADOLESCENCE—the hyphen between puberty and maturity—presents a phase of life not too well understood. Events so conspicuous as the rapid growth of childhood, the onset of menstruation at puberty and pregnancy in maturity are lacking. Independence develops, and the normal adolescent graduates from the care and supervision of the pediatrician. Ordinarily, the adolescent is not seen by a physician unless some disease or abnormality occurs; hence, the hiatus in our knowledge of normal adolescence.

Life is a changing process, varying from one person to another and from time to time in the same person. Furthermore, the human body is so readily adaptable to circumstances that it may be exceedingly difficult to predict with any degree of accuracy the response to outside influences. Yet similarity of repeated clinical observation permits an expression of opinion while one is awaiting more specific data. It is now generally understood that the structure and functions of the body, as well as the workings of the mind, may be profoundly affected by the behavior of the pituitary gland, the gonads, the adrenals and the thyroid. The action is reversible. With the stress and turmoil of the emotions in adolescence, one wonders how the endocrine glands behave as well as they do. The field of the endocrine glands cannot be isolated, but there are some instances in which the glandular role is apparent.

The general pattern of behavior of the endocrine glands centers in the pituitary. The activity of the pituitary gland is itself controlled not only by the gonadal hormones formed in response to pituitary action, but also by many additional influences. Among these influences the afferent stimuli acting through the central nervous system are important. Through the hypothalamus, the sensory organs and the emotions may profoundly affect the gonadotropic activity of the pituitary. For complete cooperation of the pituitary with the reproductive organs, the neural connections are essential. Transplantation of human ovaries and animal pituitary glands has shown, however, that these structures may function without neural connection. In relation to the present problem, the chief concern is the ability of the pituitary to control the gonads by means of the gonadotropins.

From the Department of Gynecology and Obstetrics, Henry Ford Hospital.

The chemical nature of the gonadotropins has not been determined exactly, but they are either proteins or substances closely associated with proteins. They cannot be given effectively by mouth, are not stored appreciably in the body, are inactivated when introduced into the blood stream and are excreted in the urine. Reference to the gonadotropins as the follicle-stimulating hormone and the luteinizing hormone is somewhat misleading, because separate identities have not been proved for these hormones, as they have not yet been prepared in pure form. Extracts from pituitary tissue and from the urine of castrated women are predominantly follicle stimulating, whereas extracts from the placenta and the urine of pregnant women are predominantly luteinizing. The problem of the manner of action of these hormones is complicated by the influence of the follicle-stimulating hormone and the luteinizing hormone on each other, as well as by the effect on them of the gonadal hormones. Functional disturbances may be referred, therefore, to either the pituitary gland or the ovary, or to the balance between these organs.

When the attention is limited to the gonads, the problem remains complex. A few of the disturbing factors may be mentioned.

1. The gonadal hormones have been isolated and their chemical structure determined, but correlation of molecular structure and physiologic behavior may be difficult.

2. While all the gonadal hormones produced naturally in the body have a sterol nucleus, many compounds of other constitution show similar physiologic activity.

3. The biologic effect of an organic compound introduced into the body may not come directly from the chemical substance but may be derived from its metabolic products.

4. Androgens, estrogens and progesterone may be derived from ovary, testis, adrenal gland or placenta.

5. Gonadal hormones are not stored, but are inactivated or excreted rapidly.

6. One hormone may be converted into another in the body.

7. In some proportions one hormone may cooperate with another, while in different proportions they may be antagonistic.

8. The response varies with the size and frequency of the dose of the hormone.

9. Each organ or part of an organ has its own capacity for reacting to a hormone.

10. The state of nutrition affects the response to hormones.

Delving too deeply into the intricacies of the chemistry and physiology of these hormones leads to confusion and frustration. For clinical application a simplified procedure is desirable. It is necessary, first, to explain the general pattern of sexual behavior in the adolescent and, second, to devise a simple method of studying the abnormal.

In a normal girl during childhood the gonadotropic secretion of the pituitary gland is low. Before puberty the secretion increases and continues throughout adolescence and the reproductive period. Early and late in life the follicle-stimulating hormone predominates. At puberty the relative amount of luteinizing hormone begins to increase; this corresponds to the appearance of anovulatory menstrual cycles. The rapidity of transition varies considerably, and it is not unusual therefore to find irregularity of cycles, as well as delay of ovulation, for a year or more. Balance gradually becomes established between the pituitary gland and other influences, especially the ovaries.

To explain the behavior of a gland of internal secretion, it has been helpful to compare the gland to a chemical factory. Just as the factory is constructed to produce a certain chemical when the essential materials are provided, so the secreting cell of the gland is so constituted that it will produce a specific hormone when the essential elements are provided. With use of this comparison in analyzing an apparent glandular problem, evidence is sought to establish whether the gland has developed normally and whether the quantity and quality of material provided by the blood stream are suitable for use by the gland.

Application of the method may be illustrated by citing briefly a few relatively simple cases.

ILLUSTRATIVE CASES

CASE 1.—A girl aged 18 complained of fatigue and amenorrhea for one year. Childhood and puberty had been normal. At the age of 17 her weight was average, but she had succumbed to a fad to get thin. On rigid diet, she lost 20 pounds (9 Kg.) in a few weeks. Menstruation stopped, and she had barely energy to carry on her school work. Examination showed a height of 65 inches (165 cm.), a weight of 97 pounds (44 Kg.), a basal metabolic rate of —15 per cent and mild secondary anemia. The primary and accessory reproductive organs were small. That the pituitary gland and the ovaries had developed normally was shown by the average growth and a history of normal menstruation for four years. The low basal metabolic rate suggested the possibility of hypothyroidism, but she did not tolerate even ¼ grain (0.016 Gm.) of thyroid. At the time she was first seen by me (1925), estrogenic material was available in small doses. She received injections of 2 or 3 rat units of estrogen daily, without appreciable effect. In spite of advice that she observe moderation in exercise, she persisted in finishing a course in physical education, and immediately after graduation she began to teach physical education. If she worked during the day, she was so tired that she could not go out at night. If she went out in the evening, she could not work the next day. Ten years passed in this manner, with constant fatigue and amenor-

rhea. At the age of 27 she married; immediately she began to menstruate, and in three months she became pregnant. Pregnancy, labor and lactation were normal. Menstruation was again regular until her second pregnancy. This case typifies amenorrhea due to malnutrition.

CASE 2.—A girl aged 14 complained of almost constant flowing since the onset of menstruation, at the age of 12. Definite cycles of heavy flow were present at irregular intervals. The amount of intermenstrual flow was increased by activity, so that her attendance at school was interrupted and she could not engage in athletics. She was an only child of obese parents, and her father was diabetic. The family "loved to eat." Her weight was about 40 pounds (18 Kg.) above average. Her skin was pale and pasty, and her muscles were soft and flabby. Her basal metabolic rate was repeatedly low, and blood counts showed varying degrees of secondary anemia. Development of the primary and accessory reproductive organs showed a high average for her age. Analysis of her problem indicated normal glandular function except for hypothyroidism. Administration of estrogens, progesterone and chorionic gonadotropin separately and in combination were of no avail. She tolerated 3 or 4 grains (0.19 to 0.26 Gm.) of thyroid daily. Cooperation was satisfactory except in respect to diet. Finally, at the age of 19, her pride was affected by her realization that "dates" were few and far between. About that time her father became very ill with diabetes and had to reduce his weight. These factors induced her to maintain a proper diet. She reduced to a normal weight, and menstruation became normal. Now, at the age of 25, she is attractive and alert, with no evidence of glandular dysfunction except for hypothyroidism, which is controlled easily.

CASE 3.—A girl aged 20, first seen in January 1944, complained of "flowing all the time." She had begun to menstruate at 17 and had had intermenstrual bleeding since the onset of menstruation. She was impressed with the fact that she had mumps as a child and had been led to believe that this illness was responsible for her present condition. During the preceding three years she had been under the care of several physicians and had had two curettements, which showed polypoid endometritis. An endocrinologist had given her many injections. She had taken iron preparations continuously. Examination showed pallor, a height of 62 inches (157 cm.) and a weight of 110 pounds (49.9 Kg.), with a blood pressure of 116 systolic and 84 diastolic and a pulse rate of 96. The uterus was large, and the ovaries were of average size. The accessory reproductive organs were developed normally except for scanty pubic hair. A small supply of relatively pure gonadotropins was available. For two months the follicle-stimulating hormone was given during the first half of the cycle and the luteinizing hormone during the last half. The three succeeding periods lasted eight, seven and five days, respectively. The supply of gonadotropin was then exhausted; so estrogens and progesterone were substituted. Prolonged bleeding recurred, and on Aug. 3, 1944, the patient requested that the ovaries be irradiated or the uterus removed. Since such radical treatment was refused, she sought other advice during the next year, after which she returned in the same state. At this time the blood count showed 9.0 Gm. hemoglobin per hundred cubic centimeters and 2,800,000 red cells. The weight was 101 pounds (45.8 Kg.). The blood pressure was 96 systolic and 65 diastolic. The pulse rate was 90 and the basal metabolic rate —26 per cent. Hypothyroidism was apparent and should have been detected

the year before. She tolerated up to 3 grains (0.19 Gm.) of thyroid. Within two months the duration of flow was reduced to five days and a normal amount and has remained at this level. Her height increased ¾ inch (2 cm.); her weight reached 110 pounds (50 Kg.); the blood pressure was 116 systolic and 82 diastolic. At present 2 grains (0.13 Gm.) of thyroid is the optimum dose.

When the method of analysis was applied to the cases just cited, in retrospect, normal development of the glands was established by the previous history and by examination of the primary and accessory reproductive organs. Investigation was directed, therefore, to the quantity and quality of material in the blood stream. Secondary anemia was present in each case. In the first case the anemia was associated with deficient nutrition; in the others the anemia was associated with excessive loss of blood and hypothyroidism. A low basal metabolic rate was present in all 3 cases but was not related to the function of the thyroid gland in case 1. The therapeutic test quickly established the role of the thyroid gland in cases 2 and 3. Nutritional disturbance was fundamental in the first 2 cases but was not important in the third.

Examples of abnormal development, or of lack of development, of the reproductive organs are not unusual. Generally the condition is discovered before adolescence, but frequently the best time for treatment is during this period of life.

Recognition of the emotional and endocrine relations, as well as the mechanical factors, affecting these unfortunate persons is imperative. The importance of this relation is illustrated by the case of pseudohermaphroditism reported in detail elsewhere.[1]

Briefly, the patient was deformed at birth, and her parents were so informed. They were advised to do nothing about this deformity until she had passed puberty. The parents consulted other physicians, who gave the same advice. She came to me, therefore, during her adolescence. Two complaints were uppermost in her mind. First, although she had been reared as a girl and mingled with girls, she felt embarrassment when going to the locker room because of bulging due to abnormality of the external genitalia. She had a large clitoris, but particularly troublesome was the presence of the gonads in scrotal sacs. Her second complaint was hirsutism and a tendency toward masculinity. After careful survey of her problem as a whole, it seemed important to have her retain her role as a girl. In spite of the fact that she was able to obtain sperm from the gonads, her predominating characteristics were feminine.

The particular endocrine problem in relation to this patient was the function of the gonads. Knowledge that function of the gonads was controlled by temperature was utilized in this instance. The gonads were removed from the position in the scrotum and, through an incision, were placed into the abdomen in the

1. Pratt, J. P.: Pseudohermaphrodism, Am. J. Obst. & Gynec. **40**:870-882 (Nov.) 1940.

position of ovaries. After this procedure there was no longer any production of sperm, and there were numerous manifestations that the trend toward masculinity had ceased and that femininity had increased. Subsequent results have shown that the procedure adopted was well worthwhile, as the patient developed into a brilliant person, who accepted her role as a neutral, though she associated with girls and women. By further plastic operations the cause of her complaint had been removed. Her emotional balance was greatly improved. This case is cited to show the close relation of the endocrine to the mechanical factor and to the emotional states.

Dysmenorrhea seems to be a simple problem to the laity. Information derived from advertising and popular magazines has led them to believe that the proper endocrine preparations will give complete and immediate relief. To the gynecologist the problem is complex, requiring careful exploration of the emotional relations. No endocrine preparation is specific for the relief of dysmenorrhea.

Amenorrhea is ultimately due to failure in the relation of ovary and uterus. Disturbance of development can usually be detected by examination. Assuming that development is normal, functional disturbance can be analyzed by seeking the quantitative or qualitative alteration in the blood supply of the ovary. This search leads to a complete examination, with due emphasis placed on the mental and emotional aspects. Since this procedure requires time, the busy practitioner may try a short cut. He knows that the uterus responds to ovarian secretions. Therefore, why not substitute estrogens and progesterone?

Substitution therapy is seldom effective; but while the patient is coming for "shots" week after week and month after month, nature may well make a favorable adjustment. Probably one of the greatest benefits derived from substitutional therapy is the encouragement of the patient. She feels that something specific is being done and may be much more amenable to thorough investigation. This interval of time and this approach are particularly important when the emotions play a major role.

What has been said of amenorrhea applies equally well to hypermenorrhea. In management of the latter, however, it is even more important to play for time until nature can make her readjustment.

Metabolic disturbance may be indicated by changes in texture of the skin of the external genitalia. Though commoner later in life, such a disturbance may occur during adolescence. The appearance of the skin may be the earliest symptom. The disorder of metabolism may be due to lowered sugar tolerance or to hypothyroidism or to both. The sugar tolerance and the basal metabolic rate may be normal, but the cutaneous lesion is characteristic. Treatment consists in limiting sugars and starches and giving thyroid to the point of tolerance.

Empirically, thyroid is the most useful of all glandular preparations in the treatment of gynecologic disorders of endocrine origin. The basal metabolic rate is a desirable, but not always a reliable, guide to thyroid therapy, for it is often difficult to obtain basal conditions. Furthermore, other conditions, such as the function of the pituitary gland and the state of nutrition, may influence the basal metabolic rate. The therapeutic test with thyroid may be used safely if only small doses and a few tablets are prescribed, thus necessitating the return of the patient for observation before continuing the treatment. Now and then a patient with a normal or high basal metabolic rate will tolerate considerable thyroid and another patient with a low basal metabolic rate may not tolerate any thyroid; hence, the value of the therapeutic test.

The pituitary-ovarian balance already emphasized indicates another form of treatment, namely, administration of the gonadotropins. Excellent results have been obtained with them, but the problem remains complex, for there are no pure gonadotropins. For some years chorionic gonadotropin was widely used, with many claims of excellent results; gradually, the enthusiasm for the preparation waned. Recent evidence, however, shows that when large enough doses can be tolerated favorable results may be anticipated.

2799 West Grand Boulevard.

DISCUSSION ON PAPERS ON ADOLESCENCE

DR. J. A. JOHNSTON, Detroit: Dr. Lawrence K. Frank, of New York, could not be here to speak on the "Emotional Aspects of Adolescence," so I have asked Dr. Clifford Sweet and Dr. Borden Veeder to fill in the time.

DR. C. D. SWEET, Oakland, Calif.: I shall mention only such points as patients bring to my attention. I shall not let Dr. Johnston get away with the idea that all adolescent children need is food. Their parents need to understand the situation also. The greatest difficulty in the relation of the adolescent patient to his parents is that the parents have not learned gradually to release the child and to give him increasing responsibility, without criticism, when he is not skilled in his attempts to perform unfamiliar tasks. When I talk to a mother about her daughter, I use this simple example: One of these days you will tell your daughter she must sew on her own buttons, but when the girl tries to use the needle and thread and the buttons, she will be awkward; and, if you are not careful, you will snatch it and say, "Give it to me." Then you will come to me and tell me the child is unwilling to sew on her own buttons. I try to encourage parents to realize that they must gradually release the child. When a child is 10 years of age, he is more capable of making his own decisions than he was at 6 or 7, and he is much more so at 15.

I remember a mother who brought her boy of 16 to me, saying, "Why is Johnny so insolent to me?" I asked the boy to stand up, and the mother said, "Johnny, stand up," before he had time even to move a muscle. Can one wonder that he was insolent?

I find parents need help. I shall not forget the family that came to me with a fine adolescent boy, almost through high school, who was doing well in school and in athletics. The parents complained that he was going out every night in the week. I began to inquire into the difficulty. After talking with them for a few minutes, I said, "Your boy comes home from school and says, 'I am going out,' and you say, 'No,' with the result that he goes out anyway." I advised them to give him a latch key. They did, and they had no further difficulty with him. Adolescent children are not so confident of themselves as they appear to be. If they have been brought up with an increasing amount of freedom, they will come to their parents for advice. I heard of a boy who said to his father, "I shall now make my own decisions." The father said, "I am delighted, son, it has been a great burden to have to make your decisions." The boy then said, "But I think I shall often need your advice."

I cannot sum up better than to say that parents need to be reminded that every child must go through periods of growth and development which are not agreeable to adults. I was brought up in South Dakota, and my father was a cattle man. When the calves were weaned from their mothers, they formed a separate herd. They did not go far from their adult protectors, and at night they would move in again. As soon as they matured sexually, they came back into the herd. Unfortunately, we human beings, in our planned society, cannot imitate them, but at least we can direct with understanding the behavior of the child as he grows, realizing that he must go through these various stages in order to reach adult function. We have to accept the child as he is, and we should do our best to help him become a reasonable human being.

DR. B. S. VEEDER, St. Louis: I have been asked at a moment's notice to "pinch hit" for Dr. Frank. I am not a psychiatrist or a psychologist, but a pediatrician. Adolescence is the period in which there is an inherent urge to pass from the protected period of childhood into independent adult life. The change is difficult and creates problems, because the child is not ready to leave protection behind and yet is forced to do so by his urge. There is a somewhat comparable period in early childhood with which we as pediatricians are thoroughly familiar. We know the psychologic problems which may develop in the child of from 2 to 5 years of age, when, as Dr. C. A. Aldrich puts it, the infant goes out into the world. This adjustment is sometimes hard for both the child and the parent. One expects certain problems or troubles at this time, but one does not look on them as anything abnormal. They may become real problems if the situation is not handled intelligently.

In the same way, at the period of adolescence, when real problems or troubles arise, it is frequently the result of a lack of understanding on the part of the parents rather than anything inherent in the child or the period. Adolescence is a normal period of growth, and one must be on guard to prevent abnormal deviations. In the discussion of growth it was brought out that there are differences in the age of maturation and in the chronologic age at the beginning of puberty. Dr. Johnston made the statement (in referring to physical growth) that many things parents regard as problems are really not problems or abnormalities at all. I feel that it is exactly the same with many of the psychologic problems of the adolescent. Take, for example, the girl whose menarche is a year or so in advance of the average. She has been going along with a group of the same chronologic age when her psychologic attitude toward sex is suddenly changed. It is nothing abnormal, but unless the situation is handled intelligently it may create a problem.

Another growth problem is presented by the boy who develops slowly. He becomes 14 or 15 years of age and has not "made his growth" as have the other boys in his class of the same chronologic age. He is shorter, smaller and not athletically developed. He has a feeling of inferiority, which makes him introspective and worried. He must be handled intelligently by his parents, teachers and physician and made to understand that he will keep on growing when the others have stopped. Or there is the girl who matures and grows tall early, towering above her friends of the same chronologic age. She is awkward and self conscious and if forced into social activities too prominently may react badly. These "problems" are examples of those presented by normal children in whom, through variations, from the average growth curve, not through abnormalities, all too often psychologic and behavior difficulties develop from lack of understanding and intelligent handling.

Sex is one of the most important matters of the adolescent period. It is, in fact, the very point or center of the period, and one cannot discuss adolescence without discussing sex. It is the period when the fundamental, natural biologic urge for reproduction develops, and sex becomes a matter of definite specific interest. Here, again, a large part of the problem arises from ignorance and a lack of understanding. Education in sex is important in orienting the girl or boy. We as physicians will all agree to this, but the difficulty is that we ourselves have not had good sex education, as a matter of fact, do not know much about it. We are beginning to realize that sex must be a part of every child's life from infancy, and that it consists of much more than a knowledge of sex physiology. It is something that must be brought into every aspect of the child's life in the home and in the school. Only in such a way can sex education be successful.

I sometimes wonder at the vast majority of children who come through adolescence so well adjusted. It is hard for a child, who by his growth is striving for independence, to meet successfully and adjust to the environmental handicaps in the way of taboos, customs, economic barriers and social conditions which he finds surrounding him on every side. We as pediatricians have a wonderful opportunity to help the child and the parents understand the meaning and significance of adolescence and, in this way, to prevent some of the tragedies we all too frequently encounter.

I had hoped there would be more discussion of the keto steroids, as seemingly the developments along this line offer for the first time a physiologic explanation of some of the psychologic problems.

Obituaries

HUGH KLING BERKLEY, M.D.

1889-1947

Dr. Hugh Kling Berkley was born in Woodbine, Iowa, Sept. 6, 1889, and died July 11, 1947, at the Hospital of the Good Samaritan, Los Angeles.

Dr. Berkley received his M.D. degree from the University of California Medical School in 1914. He served one year as intern at the University of California Hospital and for the next two years as resident at the Massachusetts General Hospital and the Children's Hospital in Boston. During World War I he served for two years as a captain in the Medical Corps, United States Army.

Dr. Berkley was a member of the Los Angeles County Medical Society (Pediatric Section), the Southwestern Pediatric Society (past president) and the American Academy of Pediatrics. He was a member of the staffs of the Presbyterian Hospital–Olmsted Memorial, Hollywood; the Cedars of Lebanon Hospital; the Hospital of the Good Samaritan; the California Lutheran Hospital, and the Children's Hospital. Until 1946, he was clinical professor of pediatrics in the University of Southern California School of Medicine.

Dr. Berkley began the practice of pediatrics in Los Angeles in association with Dr. Henry Dietrich. Later, Dr. Fred Glascock and Dr. Norman Nixon joined the group. While he contributed occasionally to pediatric journals, his chief interest was in his patients, in the development of the Children's Hospital of Los Angeles and in promoting good medical practice in Southern California. From 1940 to 1946 he was a member of the executive board and regional chairman of the American Academy of Pediatrics.

Dr. Berkley became associated with Children's Hospital in 1919 and was chief of staff from 1944 to 1947. Here he unselfishly and effectively devoted much energy to raising the standards of medical and hospital care. The present standing of the Children's Hospital as a leading institution in Southern California is due in no small part to his work.

In 1918 he was married to Martha Westbrook, of Los Angeles, who survives him, as do his two sons, Robert and Hugh. His mother and two brothers also survive.

J. D. L.

Correspondence

CONVULSIONS DUE TO USE OF PERTUSSIS VACCINE

To the Editor:—Recently, there has come to the attention of this committee a paper wherein convulsions are described as a complication of the use of pertussis vaccine.

We are asking the readers of the AMERICAN JOURNAL OF DISEASES OF CHILDREN to apprise us if they hear of incidents of such convulsions. Specifically, we wish to ask the following questions:

1. Did the convulsion occur while the patient was ill with something other than pertussis?
2. Was the patient given the injection regardless of whether he was ill at the time?
3. Did the convulsion occur after the first, second or third injection?
4. How long after the injection did the convulsion occur?
5. Did the child have a prior convulsion for which he was, or was not, treated?
6. Did the convulsions occur after injection of:
   - (*a*) A toxoid?
   - (*b*) An alum-precipitated toxoid?
   - (*c*) A multiple vaccine:
     - (1) Pertussis vaccine combined with diphtheria and tetanus toxoids?
     - (2) Pertussis vaccine combined with diphtheria toxoid?
     - (3) Pertussis vaccine combined with tetanus toxoid?
     - (4) Alum-precipitated pertussis vaccine combined with diphtheria and tetanus toxoids?
     - (5) Alum-precipitated pertussis vaccine combined with diphtheria toxoid?
     - (6) Pertussis vaccine alum precipitated?
7. What was the interval between injections?
8. Were any of these injections so-called booster shots?
9. If they were booster shots, what actually was injected at the time, and what had been injected previously?
10. Was there any epidemic of a disorder involving the central nervous system in the community at the time?
11. The material of which pharmaceutical manufacturer was used?
12. Is the lot number of the material used known?

If any one has any further data on the aforementioned condition, please send the report to the chairman, The Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals of the American Academy of Pediatrics.

City Hospital. JOHN A. TOOMEY, M.D., Cleveland.

News and Comment

GENERAL NEWS

Committee Formed to Study Congenital Malformations Associated with Maternal Infection During Early Pregnancy.—The relation between certain congenital malformations and rubella contracted by the mother early in pregnancy has been demonstrated. However, it is not known how often such cases occur, nor is it known whether infections other than rubellá produce malformations in the fetus.

A group of pediatricians have formed a committee to study this important problem. Serving on the committee are Dr. Stewart Clifford, Brookline, Mass.; Dr. Herbert C. Miller, Kansas City, Kan.; Dr. Clement A. Smith, Boston; Dr. Josef Warkany, Cincinnati; Dr. James L. Wilson, Detroit, and Dr. Herman Yannet, Southbury, Conn.

A questionnaire has been prepared and sent to all pediatricians, obstetricians and ophthalmologists in the United States in order that such cases as have already been seen may be reported. The study has been approved by the American Academy of Pediatrics. Financial support has been given to the study by the National Society for the Prevention of Blindness. Those not receiving questionnaires may obtain them by writing Dr. Herbert C. Miller, University of Kansas Medical Center, Kansas City, Kan.

Finnish Technologic Institute Needs Scientific and Technical Literature.—Finland has an excellent and keenly scientific-minded technical institute, *Teknillinen Korkeakoulu.* During the war its library was bombed and totally destroyed.

During a recent visit to Finland, a representative of the American Friends Service Committee discussed the situation with Dr. Martti Levon, director of the Institute, who said he would welcome gifts of scientific and technical books and periodicals from America to take the place of those destroyed. In the remarkable efforts for recovery that the Finns are making, the lack of a technical library is a serious handicap. A practical act of friendship toward a nation that holds America in high regard would be a contribution of good technical books and periodicals to this library.

Any such gifts should be marked for the Institute of Technology, Helsingfors, Finland, and sent to the Legation of Finland, 2144 Wyoming Avenue, N.W., Washington, D. C. Dr. K. T. Jutila, the Finnish minister, will arrange for their shipment to Finland.

Queens Pediatric Society Formed.—The Queens Pediatric Society has been established in Long Island City, N. Y., for the purpose of advancing the practice of pediatrics.

The officers are: president, Dr. Walter C. A. Steffen; president elect, Dr. Henry A. Reisman; secretary, Dr. Louis Appel, and treasurer, Dr. Meyeron Coe.

The organization expects to have four scientific sessions yearly.

Meeting of Pan-American Child Congress.—The Pan-American Child Congress will be held at Caracas, Venezuela, Jan. 5 to 10, 1948. One of the four sections will be "Pediatrics and Maternal and Child Health."

Announcement from UNESCO.—The United Nations Educational, Scientific and Cultural Organization announces the appointment of Dr. H. F. Helmholz as Chief Medical Consultant for Europe, under the general administrative supervision of the Director, European Headquarters in all matters of administrative policy. His duties are:

"To be responsible, in collaboration with the Chief Technical Consultant of the Fund, for the organization and direction of the European technical staff of pediatricians and other physicians, nutritionists, nurses, child welfare consultants and other professional technical staff in the fields of child feeding, health and welfare, including selection, assignment of professional or technical duties and the technical supervision of such personnel, and the general direction of nonprofessioal personnel employed in the technical division.

"In collaboration with the Chief Technical Consultant, to formulate and to recommend to the Fund policy on all technical and professional matters in the fields of child feeding, child health and welfare, and to advise the Director of the European Headquarters on such matters and to make recommendations to the Fund for the approval of plans of operation submitted by the governments as a basis for aid from the Fund.

"To act as Chief Medical Consultant in Europe and to develop the program of technical consultation service by the professional staff to European governments receiving aid from the Fund, to assign professional or technical duties in accordance with written agreements or understanding.

"To consult with governments on standards, organization and operation of special medical or other technical projects operated by the governments with the aid of the Fund and to recommend to the Fund approval of plans for such special projects.

"To advise the Fund and governments requesting aid on matters related to the training of professional personnel, including fellowships, training centers and other matters related to professional education of workers in the fields of child feeding, health or welfare.

"To collaborate with the European technical staff of the World Health Organization, the Food and Agriculture Organization and other specialized agencies and commissions of the United Nations in matters related to the health and welfare of children in Europe and the development of the Fund's program."

In explanation, Dr. Helmholz commented:

"As I see it, the first and foremost function is the supplying of protective foods, proteins in the form of milk and meats, fats and vitamins, in the following countries in which we will be working—Finland, Poland, Austria, Hungary, Czechoslovakia, Yugoslavia, Greece, Albania, Italy, Bulgaria and Rumania.

"In addition, we are hoping to get started on some sort of constructive program to combat tuberculosis and venereal disease. As a third item, we will be working toward a permanent program for international cooperation in the development of international training centers for doctors, nurses, health officers and administrators, and social service workers for child health and welfare."

PERSONAL NEWS

New Director of Children's Hospital, Boston.—Dr. Guy W. Brugler, assistant director of University Hospitals, Cleveland, will become director of the Children's Hospital, Boston, on Nov. 1, 1947.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

SULFADIAZINE RESISTANT STRAINS OF BETA HEMOLYTIC STREPTOCOCCI: APPEARANCE DURING THE COURSE OF SULFADIAZINE PROPHYLAXIS AT A LARGE NAVAL TRAINING CENTER; EPIDEMIOLOGY UNIT NUMBER 22, J. A. M. A. **129**:921 (Dec. 1) 1945.

After approximately three months of successful use of sulfadiazine in prophylaxis of infections of the respiratory tract at a large naval training center, the effectiveness of this measure became progressively less, and eventually a major epidemic of streptococcic disease occurred.

An increase in the dose as high as 2 Gm. daily did not prevent the occurrence of streptococcic diseases, and it was the impression of the medical officers at the center that the drug had lost its therapeutic value for these infections.

Loss of the prophylactic value of sulfadiazine was originally associated with an absolute and a relative increase in frequency of group A, type 19 infections. Later, group A, type 17 infections became relatively frequent. These two types of the streptococcus were shown by laboratory methods to be resistant to sulfonamide drugs in vitro. Other types of streptococci, with the exception of type 3 in a few cases, were not resistant to sulfonamide compounds.

The proportion of sulfadiazine-resistant strains was greater in the recruit camps receiving sulfadiazine prophylaxis than in those not receiving the drug. There was some suggestive evidence, but no definite proof, that in the presence of sulfadiazine-resistant strains, sulfadiazine prophylaxis tended to increase streptococcic infection, particularly scarlet fever.

BAIRD, Wauwatosa, Wis.

Metabolism; Infant Feeding; Milk and Other Foods

VARIABILITY IN THE CALCIUM METABOLISM AND CALCIUM REQUIREMENTS OF ADULT HUMAN SUBJECTS. F. R. STEGGERDA and H. H. MITCHELL, J. Nutrition **31**:407 (April) 1946.

From their experiments, the authors reported that the average calcium requirement of the adult human subject was 644 mg., or 9.21 mg. per kilogram of body weight, per day.

FREDEEN, Kansas City, Mo.

THE ABSORPTION OF RADIOACTIVE IRON BY CHILDREN 7-10 YEARS OF AGE. W. J. DARBY, P. F. HAHN, M. M. KASER, R. C. STEINKAMP, P. M. DENSEN and M. B. COOK, J. Nutrition **33**:107 (Jan. 10) 1947.

The authors made determinations of the absorption of iron in 176 school children 7 to 10 years of age, which indicated a mean uptake of 7.75 to 17.75 per cent of a test dose of 2 mg. of ferrous iron. The median intakes were slightly lower. The uptake was found to be correlated with the estimated yearly increases of body iron during growth; it was not correlated in these children with other factors tested for, such as economic status of the group, dietary intake as estimated, hemoglobin level

or general nutritive state. It was estimated from these data that the mean daily requirement of absorbable iron is 2.3 to 3.8 mg. for children of this age group.

FREDEEN, Kansas City, Mo.

THE EFFECT OF CRUDE LECITHIN ON THE COEFFICIENT OF DIGESTIBILITY AND THE RATE OF ABSORPTION OF FAT. VIRGINIA AUGUR, HILDA S. ROLLMAN and HARRY J. DEUEL JR., J. Nutrition **33**:177 (Feb. 10) 1947.

From their experiments, the authors concluded that the addition of lecithin to cottonseed oil or to a hydrogenated cottonseed oil definitely lowers the susceptibility to diarrhea produced by administration of a large dose of these fats to rats. Fats containing one-sixth or one-fifth crude lecithin are absorbed more rapidly than similar fats without any added phosphatide. A considerably larger portion of the lipid in all cases was excreted as soaps rather than as neutral fat and fatty acids.

FREDEEN, Kansas City, Mo.

A COMPARISON OF THE COEFFICIENT OF DIGESTIBILITY AND THE RATE OF ABSORPTION OF SEVERAL NATURAL AND ARTIFICIAL FATS AS INFLUENCED BY MELTING POINT. MARY E. CROCKETT and HARRY J. DEUEL JR., J. Nutrition **33**:187 (Feb. 10) 1947.

The authors studied the digestibility of various fats. The digestibility coefficients obtained were: margarine (melting point, 34 C.), 97.0 per cent; "crisco" (melting point, 43 C.), 97.3 per cent; prime steam lard (melting point, 37 C.), 96.6 per cent; bland lard (melting point, 48 C.), 94.3 per cent; hydrogenated lard (melting point, 55 C.), 63.2 per cent, and hydrogenated lard (melting point, 61 C.), 21.0 per cent. There was no evidence that any of these fats produced abnormal physiologic effects, such as diarrhea.

FREDEEN, Kansas City, Mo.

Vitamins; Avitaminoses

METABOLISM OF NICOTINAMIDE, NICOTINIC ACID AND DIETHYLAMIDE OF NICOTINIC ACID (CORAMINE) BY NEWBORN AND PREMATURE INFANTS. R. A. COULSON and C. A. STEWART, Proc. Soc. Exper. Biol. & Med. **61**:364 (April) 1946.

A series of 24 newborn infants maintained on a formula of evaporated milk were given 100 mg. of nicotinamide by mouth, and the urine was studied quantitatively for excretion of methochloride. These infants eliminated 10 times the amount (36.7 mg.) of methochloride as that of 23 control infants in a twenty-four hour period. Other groups of infants (15, 11 and 11) were given repeated doses of nicotinamide, nicotinic acid, and nikethamide. It appeared that these infants, like adult subjects, were able to methylate the preformed nicotinamide easily and rapidly, whereas they converted nikethamide slowly and less completely, first to nicotinamide and then to nicotinamide methochloride. Nicotinic acid occupies an intermediate position. Study of 15 premature infants indicated that they eliminated less nicotinamide methochloride than full term infants under the same conditions. Administration of methionine (0.3 Gm. on two occasions) did not affect excretion of nicotinamide methochloride following administration of 100 mg. of nicotinamide. Two infants were given 200 mg. of nikethamide, and excretion studies indicated that nikethamide is normally converted to nicotinamide and excreted as nicotinamide methochloride. These excretion studies suggested that the tissues of newborn infants contain an appreciable store of nicotinamide at the time of birth.

HANSEN, Galveston, Texas.

CLASSIFICATION OF AND DIAGNOSTIC METHODS FOR RICKETS. S. O. DOLITZKY, Pediatria **52**:53 (March) 1944.

In accordance with a resolution passed by the Third Congress of Soviet Pediatricians, cases of rickets were classified according to the degree of severity of the disease into three groups: (1) mild, (2) moderately severe and (3) severe rickets. The diagnostic methods used are described, and the symptoms of the various stages of rickets are discussed.

BODER, Los Angeles.

Newborn

ACUTE ANEMIA OF THE NEWBORN INFANT: REPORT OF A CASE. P. BERTOYE, D. PICKARD and A. MEYNADIER, Arch. franç. de pédiat. **3**:82, 1946.

The relative infrequency and the still fluid classification of acute anemia of the newborn infant make it incumbent on the clinician to report his observations. Such a case is reviewed as an introduction to the consideration of anemias at the threshold of life.

A girl 10 days old was admitted to the clinic at Lyon with a history of icterus which developed thirty-six hours after birth but rapidly disappeared, leaving the baby extremely pale and weak. The family history revealed that the mother, in excellent health herself, had had two previous pregnancies; the first child was a boy, now 4 years of age and in excellent health; the second succumbed to atresia of the bile ducts on the fourth day. This diagnosis was confirmed by autopsy. Examination of the case in question showed an infant with great respiratory embarrassment and with skin of a waxy tint. There were 430,000 red blood cells, the hemoglobin value was 15 per cent (2.3 Gm.) and there were 8,300 white blood cells, with 13 per cent polymorphonuclear cells, 32 per cent small lymphocytes, 2.5 per cent large lymphocytes, 42.5 per cent monocytes, 1 per cent metamyelocytes, 4.5 per cent monoblasts, 3 per cent plasmocytic monocytes, 1 per cent typical plasmocytes and 0.5 per cent eosinophils. There was slight anisocytosis.

After puncture of the external tuberosity of the superior tibial epiphysis a myelogram was studied with the following result: granular series, 52.5 per cent, including polymorphonuclear cells (20 per cent), eosinophils (2.5 per cent), metamyelocytes (14 per cent), myeloneutrophils (10 per cent), promyelocytes (3.5 per cent) and myeloblasts (2.5 per cent); lymphoid series, 22.5 per cent, including small lymphocytes (20 per cent) and large lymphocytes (2.5 per cent); monocytic series 20 per cent, including monocytes (16.5 per cent), monoblasts (2 per cent) and plasmocytes (1.5 per cent); stem cells, 3 per cent, including hemocytoblasts (2.5 per cent) and hemohistioblasts (0.5 per cent), and normoblasts, 2 per cent.

The marrow was poor in elements, with basement membrane clear and nongranular. No megakaryocytes were found.

In spite of active treatment, including the use of oxygen, extract of liver, "syncortyl" (a parenteral preparation of desoxycorticosterone acetate) and a transfusion, the infant succumbed twenty-four hours after admission. A summary of the autopsy report confirmed the diagnosis of acute anemia of the newborn developing under the mask of a transient icterus. From a hematologic viewpoint, there was intense destruction of the red cells with no effort at regeneration. From an anatomic study, there was medullary aplasia, limited to the red elements and resulting in almost complete disappearance of the cells. There were concomitant disturbances of ossification and intrasplenic hyperhemolysis with areas of siderosis in the liver and spleen.

AMESSE, Denver.

RETICULOCYTIC CRISES IN THE NEWBORN. D. MARCELLO BOLLETTI and D. LUIGI VILLANI, Riv. clin. pediat. **45**:1, 1947.

The authors studied in 20 normal newborn children the behavior of the red blood cells, reticulocytes, nucleated cells of the red series and the Heilmeyer scheme during the first days of life.

They observed that the number of red blood cells and reticulocytes increases almost constantly after birth, attaining the greatest number in the first twenty-four hours of life and after that decreasing. On the other hand, Heilmeyer's scheme deviates to the left at birth and deviates always to the right afterward, and the cells of the red series decrease progressively after birth.

A possible explanation of these phenomena is amply discussed.

FROM THE AUTHORS' ABSTRACT.

MILD ERYTHROBLASTOSIS FETALIS. S. I. DE VRIES, Nederl. tijdschr. v. geneesk. **91**:13 (Jan. 4) 1947.

On 85 normal children, born at full term, whose mothers were Rh positive, a complete morphologic blood test was made to determine the normal hemogram and the number of reticulocytes usually present. The same examination was made on 35 apparently normal Rh-positive newborn infants, whose mothers were Rh negative. For a high percentage of the infants the blood picture showed the characteristics of a hemolytic anemia, whereas the number of reticulocytes was significantly increased. Furthermore, it was possible to demonstrate the presence of Rh antibodies in the maternal blood.

These cases of incipient erythroblastosis fetalis confirm the opinion that the cause of this disease is closely connected with antagonism concerned with the Rh factor.

VAN CREVELD, Amsterdam, The Netherlands.

Acute Infectious Diseases

CHANGES IN LEUKOCYTES BETWEEN THE CRISES OF MALARIA IN CHILDREN. SABIHA CURA, Ann. pædiat. **168**:195 (April) 1947.

Like other investigators, the author noted a relative decrease in the number of leukocytes at the height of the fever in attacks of malaria and an increase when the temperature was lowest. In complicated cases no leukopenia was observed. The eosinophils nearly always disappeared and remained absent even far into convalescence. They were present in ascariasis during attacks of fever. During fresh infections the percentage of mononuclear cells was not more than 3. In cases of chronic infection it was not more than 10. The number of mononuclear cells did not always increase in malaria. The polymorphonuclear leukocytes increased and decreased in direct relation to the changes in temperature.

Two days after the parasites had disappeared from the blood the number of polymorphonuclear leukocytes decreased with the falling temperature. At the same time, the author observed a relative lymphocytosis of three to four days' duration. After that there was an increase in polymorphonuclear leukocytes with a diminishing number of lymphocytes. The number of lymphocytes decreased during attacks of fever and increased during the periods of apyrexia. Thus the lymphocytic reaction runs an inverse course to that of the polymorphonuclear leukocytes. If one were to construct the curves for temperature and for the numbers of polymorphonuclear leukocytes and lymphocytes, it could be shown that the curve for tempera-

ture and the curve for polymorphonuclear leukocytes run a parallel course, whereas the curve for lymphocytes runs inversely to them.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

CHRONOLOGIC ORDER OF ALLERGIC EXUDATIVE PROCESSES IN PRIMARY TUBERCULOUS INFECTION. G. CURCI and M. GEMMI, Pediatria **55**:87 (Jan.-March) 1947.

Through observations on 80 cases of multiple and successive processes of an allergic exudative character, the authors established the chronologic order with which the variously localized processes follow one another. From their researches, it appears that the various allergic manifestations have a well defined position in time, owing to the successive appearance of allergic phases of the different organs and tissues. In their conclusion, they point out and analyze the probable causes of the variations in behavior.

FROM THE AUTHORS' ABSTRACT.

CHILDREN WITH JUVENILE DEMENTIA PARALYTICA AND NONSYPHILITIC SIBLINGS: REPORT OF TWO CASES. HANS ZELLWEGER, Helvet. pædiat. acta **1**:341 (May) 1946.

Two cases of juvenile dementia paralytica in the terminal stage are described. In the first case all the siblings were healthy and seronegative, while in the second case an elder sister, begotten after the infection of the parents, was healthy but a younger sister had congenital syphilis. The literature is reviewed and the differences between dementia paralytica in the adult and the disease in the child are pointed out. Children with juvenile dementia paralytica often show retardation in mental and physical development, even before onset of the disease. Apoplectiform attacks and epileptiform convulsions are oftener associated with the juvenile than with the adult form. Simple dementia predominates in the psychomental changes. The prognosis is much less favorable than it is for the progressive dementia paralytica of adults. In many families neurosyphilis appears in an incidence higher than average.

FROM THE AUTHOR'S ABSTRACT.

CLINICAL AND PATHOLOGIC OBSERVATIONS IN CASES OF CONGENITAL SYPHILIS. C. DE LANGE, Maandschr. v. kindergeneesk. **14**:137 (May) 1946.

The author presents the clinical histories and results of anatomicopathologic investigation in 3 cases of congenital syphilis, in which the diagnosis had not been made until the children were hospitalized. The author stresses the fact that icterus and ascites are rare symptoms of congenital syphilis, contrary to the prevailing opinion of general practitioners.

VAN CREVELD, Amsterdam, The Netherlands.

Diseases of the Blood, Heart and Blood Vessels and Spleen

COARCTATION OF THE AORTA. G. H. REIFENSTEIN, S. A. LEVINE and R. E. GROSS, Am. Heart J. **33**:146 (Feb.) 1947.

The authors reviewed 104 cases of the adult type of coarctation of the aorta seen at autopsy in persons 2 years of age or older.

Sixty-one per cent of the patients died before or during their fortieth year of life, the average age at death being 35 years.

The causes of death were as follows: incidental causes, 26 per cent; rupture of the aorta, 23 per cent; bacterial endocarditis or aortitis, 22 per cent; congestive failure, 18 per cent, and intracranial lesions, 11 per cent.

Coarctation of the aorta should be diagnosed in early life, for it is then that the best results are obtained by surgical resection of the area of coarctation.

GIBSON, Chicago.

CHEMICAL, CLINICAL AND IMMUNOLOGICAL STUDIES ON THE PRODUCTS OF HUMAN PLASMA FRACTIONATION: XXXII. THE COAGULATION DEFECT IN HEMOPHILIA. AN IN VITRO AND IN VIVO COMPARISON OF NORMAL AND HEMOPHILIC WHOLE BLOOD, PLASMA AND DERIVED PLASMA PROTEIN FRACTIONS. JESSICA H. LEWIS, C. S. DAVIDSON, GEORGE R. MINOT, J. P. SOULIER, H. J. TAGNON and F. H. L. TAYLOR, J. Clin. Investigation **25**:870 (Nov.) 1946.

Normal and hemophilic plasmas were fractionated by the department of Physical Chemistry of Harvard Medical School. The data showed that the prothrombin and fibrinogen contents were identical in the two plasmas and that they were similarly distributed in the corresponding fractions. Most of the fibrinogen was in fraction I; most of the prothrombin was in fraction II + III, while fraction V was almost pure albumin.

Proteolytic activity was determined by incubating chloroform-activated plasma and fractions with a casein substrate and then measuring the percentage of increase of nonprotein nitrogen produced. Peak activities occurred after twelve hours and lasted six days, and there was no significant difference between the hemophilic and the normal curves. Fractions I, II + II and IV—1 had most of the proteolytic activity.

Normal plasma and normal fractions I, II + III and IV—1 contained a substance capable of shortening the coagulation time of hemophilic plasma. This substance was absent in hemophilic plasma and in its corresponding fractions.

The authors stated that the defect in hemophilia probably resides in one or more of the precursors of thrombin. This defect could not be identified with fibrinogen, prothrombin or the proteolytic enzyme, nor did it alter the Tiselius diagram.

BRODSKY, Cincinnati.

CHEMICAL, CLINICAL AND IMMUNOLOGICAL STUDIES ON THE PRODUCTS OF HUMAN PLASMA FRACTIONATION: XXXIII. THE COAGULATION DEFECT IN HEMOPHILIA: THE EFFECT IN VITRO AND IN VIVO ON THE COAGULATION TIME IN HEMOPHILIA OF A PROTHROMBIN AND FIBRINOGEN-FREE NORMAL PLASMA AND ITS DERIVED PROTEIN FRACTIONS. JESSICA H. LEWIS, J. P. SOULIER and F. H. L. TAYLOR, J. Clin. Investigation **25**:876 (Nov.) 1946.

Normal plasma was heated to 56 C. for two and one-half minutes. After heating there was no clottable fibrinogen and only a trace of prothrombin in the plasma. No fibrinogen or thrombin was discovered in any of these plasma protein fractions, and in fractions I, II + III and IV only traces of prothrombin were detected.

Hemophilic clot-promoting activity was measured by hemophilic plasma recalcification and whole blood coagulation times. The prothrombin and fibrinogen-free plasma obtained by heating still showed definite hemophilic clot-promoting powers. The fractions derived showed pronounced activity in fractions I and II + III and were similar to fractions obtained from normal plasma.

Fraction I from normal plasma was heated at 56 C. for four minutes, yielding a supernatant fluid free of fibrinogen and with a low protein content. When injected intravenously, it was as active in reducing the clotting time of a hemophilic patient as the same fraction I before heating.

BRODSKY, Cincinnati.

GAUCHER'S DISEASE (CEREBROSIDE THESAURISMOSIS) OCCURRING IN EARLY CHILDHOOD. MAURO AMATO, Pediatria **55**:31 (Jan.-March) 1947.

After classifying Gaucher's disease with the thesaurismoses, the author reports 2 cases which he observed in infants. The diagnosis was made by splenobioptic studies.

After reviewing the existing literature on this subject, he calls attention to the evolution and the clinical manifestations which characterize this disease when it occurs in early infancy.

FROM THE AUTHOR'S ABSTRACT.

TREATMENT OF ACUTE BACTERIAL PERICARDITIS WITH PURULENT EFFUSION. AMEDEO BILLI, Riv. clin. pediat. **45**:154 (March) 1947.

The author reports a case of acute bacterial pericarditis with purulent effusion in a girl 4 years old. Surgical treatment was resorted to because of signs of imminent cardiac embarrassment, not influenced by a previous puncture of the pericardium or by treatment with penicillin.

In this article, the author discusses the displacement of the mediastinum in cases of exudative pericarditis and the indications for surgical intervention in this disease. Recovery followed operation in the author's case.

FROM THE AUTHOR'S ABSTRACT.

ACUTE HEMOLYTIC ANEMIA (LEDERER-BRILL ANEMIA) WITH EXTENSIVE PHAGOCYTOSIS OF ERYTHROCYTES IN THE PERIPHERAL BLOOD. ROBERT F. LANDOLT, Helvet. pædiat. acta **1**:335 (May) 1946.

A case of fatal acute hemolytic anemia (Lederer-Brill anemia) in a girl aged 6 years and 7 months is reported. In addition to a highly increased fragility of the erythrocytes, a great number of monocytes were observed in the peripheral blood which were actively phagocytosing erythrocytes and which probably came directly from the reticulum.

FROM THE AUTHOR'S ABSTRACT.

Diseases of Nose, Throat and Ear

LATERAL SINUS THROMBOSIS DUE TO ACUTE MASTOIDITIS: RECOVERY WITH PENICILLIN. JAMES CROOKS, Proc. Roy. Soc. Med. **39**:588 (Aug.) 1946.

A boy 7 years of age had had earache for about a week and a discharge from the ear for three days. His mother had noticed a lump in his neck high up on the right side which had been present one day. His temperature had not been very high. On admission to the hospital he was acutely ill, and examinations revealed mastoiditis on the right side with an abscess in the neck below the tip of the mastoid process. At operation the lower portion of the lateral sinus was observed to be collapsed and thrombosed, with a perisinal abscess leading to the abscess in the neck. The child was given penicillin and "sulfamezathine" (dimethyl derivative of sulfadiazine) in full dosage and made an uninterrupted recovery.

WILLIAMSON, New Orleans.

Diseases of Lungs, Pleura and Mediastinum

EFFECT OF VARIOUS DRUGS ON EXPERIMENTAL ASTHMA PRODUCED IN GUINEA PIGS BY EXPOSURE TO ATOMIZED HISTAMINE. EARL R. LOEW, MARGARET E. KAISER and V. MOORE, J. Pharmacol. & Exper. Therap. **86**:1 (Jan.) 1946.

The authors found that the effective drugs, in order of their potency, were epinephrine, diphenhydramine hydrochloride ("benadryl hydrochloride") and meperidine hydrochloride ("demerol hydrochloride"), atropine, papaverine and aminophylline. Ephedrine, among many others, was ineffective, possibly because its stimulation of respiration increased the amount of histamine inhaled, thereby completely masking the bronchodilator properties of ephedrine.

PILCHER, Cleveland.

BRONCHIECTASIS INVOLVING ALL LOBES OF BOTH LUNGS TREATED BY LOBECTOMY AND MULTIPLE SEGMENTAL RESECTIONS. R. S. PILCHER, Proc. Roy. Soc. Med. **39**:594 (Aug.) 1946.

The patient, a girl aged 10 years, was admitted to the hospital with a history of persistent cough since she was 4 years of age, when she had measles and whooping cough. She was admitted for investigation, as she was thought to have bronchiectasis. Bronchograms showed extensive bronchiectasis of all lobes. In spite of all the lobes being affected, there were many segments free of the disease, and it was decided to attempt radical treatment by multiple segmental resections. The child was prepared for operation by postural drainage and breathing exercises, and she had her tonsils and adenoids removed. The first operation on the chest was not undertaken until more than a year after the diagnosis was made. The three operations which were performed are reported in detail. A postoperative bronchogram showed the residua of both lobes reexpanded and no bronchiectasis.

WILLIAMSON, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

A COMPARISON OF THE CEPHALIN-CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS IN PATIENTS WITH EXPERIMENTALLY INDUCED INFECTIOUS HEPATITIS. W. PAUL HAVENS JR. and RUTH E. MARCK, J. Clin. Investigation **25**:816 (Nov.) 1946.

Previously healthy male human volunteers contracted infectious hepatitis experimentally after inoculation with or ingestion of stool material from a United States Army soldier who had had infectious hepatitis in Sicily in 1943. The filtrable agent produced the disease in 27 out of 40 volunteers. Four hundred cephalin-cholesterol flocculation tests according to the method of Hanger (*J. Clin. Investigation* **18**:261, 1939) and 400 thymol turbidity tests according to the method of Maclagen (*Nature, London* **154**:670, 1944) were done on the serums of the 27 volunteers.

During the incubation period, which ranged from fifteen to twenty-eight days, the results of both tests were negative. In the first five days of fever, before jaundice, the serums of 20 out of 45 of the subjects gave positive reactions to the cephalin-cholesterol flocculation test, while but 8 out of 43 of the same serums reacted positively to the thymol turbidity tests. Both tests gave equally positive reactions during the active icteric phase, but the cephalin-cholesterol test became positive earlier than the thymol turbidity test, and also gave a normal response

earlier. This disagreement in positivity between the two tests early in the pre-icteric phase and later in the convalescent phase suggested to the authors that the mechanisms underlying the two tests may be different. BRODSKY, Cincinnati.

THE THERAPY OF NOMA (GANGRENOUS STOMATITIS). G. ROBERTO BURGIO, Riv. clin. pediat. **45**:34, 1947.

The author reports a case of noma (gangrenous stomatitis) following typhoid in a 7 year old child, which was successfully treated.

Besides local therapy, the patient was given douches of potassium permanganate and of arsphenamine and applications of sulfonamide compounds, while general therapy was started with arsphenamine, sulfathiazole, nicotinic acid, intravenous injections with a solution of a glucoside, injections of insulin, frequent blood transfusions and injections of antipyogenic vaccine.

An intravenous injection of typhoid vaccine produced a fall in temperature and rapid disappearance of the symptoms of typhoid.

The therapy of noma is discussed. FROM THE AUTHOR'S ABSTRACT.

DOES EPIDEMIC HEPATITIS RESULT IN ACUTE YELLOW ATROPHY OR IN HEPATIC INSUFFICIENCY WITH BILIARY (FAMILIAL) CIRRHOSIS OF THE LIVER? E. GLANZMANN and OSWALD MEIER, Helvet. pædiat. acta **1**:281 (May) 1946.

The question asked in the title of this paper was answered as follows: The first case was not one of epidemic hepatitis terminating in acute yellow atrophy of the liver, but one of hepatic insufficiency with biliary cirrhosis of the liver, which was provoked by the probable intercurrent development of epidemic hepatitis, thus explaining the discrepancy which existed between the rapid clinical development and the much older anatomicopathologic modifications.

The fatal and nonicteric course of the cirrhosis of the liver in the 8 year old sister would lead one to suspect the constitutionally weak parenchyma of the liver, although, etiologically, an intrafamily infection with abdominal tuberculosis may, perhaps, have provoked the cirrhosis of the liver. In connection with the second case, it is of interest to note that Herman also observed a case of subacute yellow atrophy of the liver in a 10 year old child, in which the abdominal manifestations led him to perform an operation for acute appendicitis, without, however, any fatal deterioration at this early stage. The first observation shows that the clinical picture does not permit, a priori, an anatomic diagnosis of acute yellow atrophy of the liver, but allows only a functional diagnosis, i. e., hepatic insufficiency.

FROM THE AUTHORS' ABSTRACT.

Nervous Diseases

NEW DRUGS IN EPILEPSY THERAPY. WILLIAM G. LENNOX, Am. J. Psychiat. **103**:159 (Sept.) 1946.

An evaluation of the efficacy of trimethadione ("tridione") and "mesantoin" (methylphenylethyl hydantoin) in the treatment of epilepsy leads the author to conclude that trimethadione is effective in controlling the petit mal triad—pyknolepsy, myoclonic jerks and akinetic seizures. Grand mal attacks are not influenced or are made worse by this drug.

"Mesantoin" gives poor results in cases of petit mal but appears superior to diphenylhydantoin sodium in control of major seizures. The side effects of "mesantoin" are distinctly less in frequency and severity. JAHR, Omaha.

THE GENETICS OF EPILEPSY. WILLIAM G. LENNOX, Am. J. Psychiat. **103**:457 (Jan.) 1947.

The author maintains that if knowledge of epilepsy is to be systematized speculation on its hereditary phases must be replaced by tabulation, with proper adjustment of the various factors involved in the tabulating. He suggests that knowledge be built on the following data: (1) incidence of epilepsy in the various age groups of the general population; (2) incidence of seizures among blood relatives of persons with epilepsy, with attention to possible genetic or acquired factors; (3) incidence of seizures in relatives in whom the hereditary factor is known, i. e., monozygotic twins, and (4) incidence of asymptomatic cerebral dysrhythmia in the general population, in persons with epilepsy and in co-twins or other relatives of persons with epilepsy.

Reliable statistics on the incidence of epilepsy and its age group distribution in the general population are not available. Among near relatives of 1,115 employees of state hospitals, 0.66 per cent had experienced one or more seizures. An estimate for general population is 0.5 per cent. The incidence of seizures among relatives of persons with epilepsy is 2.7 per cent. Therefore, any given child of the average person with epilepsy has about 39 chances out of 40 of being "normal," an incidence similar to that for diabetes. Among the 2,130 patients in the author's series, only 17 per cent knew of any blood relatives who were similarly afflicted. Also, the incidence of epilepsy among relatives is three times as great in the group with acquired, symptomatic epilepsy as it is in the general population. Thus, an essential and genetic influence is present, even in persons with the acquired type.

Epilepsy begins early in patients of the female sex, in spite of the fact that male infants are more prone to birth injuries. The disproportion is explained on the basis of the tendency of conditions which are predominantly genetic to manifest themselves early in life. This study shows, indeed, that such patients had an unusual number of relatives with epilepsy.

An analysis of 55 epileptic twins showed that of the monozygotic group, both co-twins were epileptic in 94 per cent of twins without evidence of cerebral damage and in 17 per cent of those with evidence of cerebral involvement. Only one of the pairs of dizygotic twins had epilepsy in both co-twins.

As to the electroencephalogram, it is an inherited pattern, the author states, and at present is limited as to its practical value, mainly because cortical electroactivity is a fluid trait.

The author concludes that epilepsy per se is not inherited but that a tendency or a predisposition to it is inherited.

JAHR, Omaha.

GLIOMA OF THE OPTIC CHIASMA. J. MINTON, Proc. Roy. Soc. Med. **38**:566 (Aug.) 1945.

In the case reported, both the eyes were blind with prominent proptosis and deviation downward and outward. The disks were examined with use of an anesthetic before operation. The appearance of both is described in the author's report. At operation for excision of the right eye, the optic nerve was observed to be surrounded by an encapsulated tumor which was larger than the eyeball. The tumor was freely detached from the surrounding orbital tissue, but its posterior limit could not be defined, as the tumor seemed to be coming from the anterior cranial fossa. The eye with its adherent mass was removed. The author believed the tumor to be a glioma of the optic chiasm which grew through the optic foramens into both orbits.

WILLIAMSON, New Orleans.

INFLUENZAL MENINGITIS. DONALD PATERSON, Proc. Roy. Soc. Med. **39**:589 (Aug.) 1946.

The patient, aged 13 months, was admitted to the hospital as an emergency case after having collapsed in the morning at a nursery school. The temperature was 100 F. and the pulse rate 144 per minute. The child was toxic and slightly cyanosed. The neck was rigid and the Kernig sign positive. The cerebrospinal fluid was turbid and yielded Hemophilus influenzae type B on culture. The child was given sulfadiazine, 1 Gm. every quarter-hour. Treatment was stopped after 30 Gm. was given. A total of 252,000 units of penicillin was administered intramuscularly and 23,000 units intrathecally, with anti-Hemophilus-influenzae type B rabbit serum in an amount equivalent to 32 mg. of precipitated antibody, given intravenously. On the second day of treatment, the child was greatly improved. By the twelfth day he was almost completely well, and on the seventeenth day he was discharged from the hospital. A lumbar puncture was performed every two or three days. Analysis of the cerebrospinal fluid is given in the report.

WILLIAMSON, New Orleans.

INFLUENZAL MENINGITIS. BERNARD SCHLESINGER, Proc. Roy. Soc. Med. **39**:589 (Aug.) 1946.

A patient aged 17 months, fourteen days before admission to the hospital, had otitis media in the right ear and a paracentesis had to be performed. Examination on admission to the hospital showed a pale, miserable child with rigidity of the neck. The fundi of the eyes were normal. A small, nodular postcervical gland was observed. The cerebrospinal fluid was turbid but not under pressure. The white blood cell count was 27,000, with 81 per cent polymorphonuclear leukocytes. The patient was given sulfadiazine, penicillin intramuscularly and intrathecally and anti-Hemophilus-influenzae rabbit serum and was discharged from the hospital in about three weeks. A table showing the daily analysis of the cerebrospinal fluid and the doses of drugs given in treatment accompany the report.

WILLIAMSON, New Orleans.

ELECTROENCEPHALOGRAPHY IN STUDY OF CONVULSIVE STATES. P. CHAUCHARD, Presse méd. **53**:454 (Aug. 25) 1945.

The author describes in detail the neurophysiology of various convulsive states. Electroencephalography enables one to distinguish between two distinct forms of disturbance, one in which there is stimulation of cortical centers, which may be widespread, and the other in which the centers above the midbrain are inhibited (causing coma) and the lower centers are stimulated (causing convulsions). Ordinary epilepsy is of the former sort, and therefore is amenable to treatment with a drug such as diphenylhydantoin sodium ("dilantin sodium").

DAFFINEE, Melrose, Mass.

ACUTE MENINGITIS IN CHILDREN IN ROSARIO. LUIS PRUSS, Rev. Soc. pediat. d. litoral **10**:267 (Sept.-Dec.) 1945.

During the years 1936 to 1942, 176 cases of meningitis were observed. The author discusses the symptoms and treatment of the various forms of meningitis. Comprehensive statistics concerning the occurrence and age distribution are added.

SOLMITZ, Chicago.

DIFFUSE JUVENILE FAMILIAL CEREBRAL SCLEROSIS (TYTE-SCHOLZ DISEASE). CORNELIA DE LANGE, Ann. pædiat. **168**:138 (March) 1947.

The author studied the brains of 2 patients with the juvenile type of diffuse cerebral sclerosis. Earlier, she was able to examine the brain of a child belonging to another family. The histologic details were similar in every respect; only in the localization of the process were there differences.

One may assume almost with certainty that the cause of diffuse sclerosis is not to be found in an exogeneous factor, such as a virus infection, or in an allergic process, but is basically the manner in which the brain reacts to certain influences. Thus it is an endogenous matter. In substantiating this point of view, the histologic studies and the hypotheses of the Danish investigators Eilarson and Neel are highly important.

FROM THE AUTHOR'S ABSTRACT.

Psychology and Psychiatry

FURTHER OBSERVATIONS ON THE USE OF TRIDIONE [TRIMETHADIONE] IN THE CONTROL OF PSYCHOMOTOR ATTACKS. RUSSEL N. DE JONG, Am. J. Psychiat. **103**:162 (Sept.) 1946.

This report is based on an analysis of 60 cases in which trimethadione (N. N. R.) ("tridione") was used alone or in combination with other drugs commonly used in the treatment of epilepsy. Trimethadione used alone was found helpful in the control of psychomotor seizures in several instances. It was found most helpful when combined with diphenylhydantoin sodium and/or phenobarbital.

Toxic symptoms were infrequent. Their occurrence does not constitute a contraindication to the use of the drug.

JAHR, Omaha.

THE PREVENTION OF PROBLEM BEHAVIOR. HERBERT C. ARCHIBALD, Arch. Pediat. **63**:216 (May) 1946.

The author presents an extremely brief and generalized discussion of some of the common unfavorable environmental conditions which are conducive to the development of behavior problems. Deviations of behavior within the limits of "normal" are mentioned as not being significant of emotional or environmental conflict. No bibliography is given.

GRULEE JR., Minneapolis.

Diseases of the Genitourinary Tract

CONGENITAL BILATERAL MEGALOURETERS WITH HYDRONEPHROSIS: A REMARKABLE FAMILY HISTORY. HELEN MACKAY, Proc. Roy. Soc. Med. **38**:567 (Aug.) 1945.

This anomaly was reported in a girl aged 4¾ years. Her paternal grandfather had had a nephrectomy for calculous pyonephrosis, and in the patient's family of 7 siblings 5 were known to have had congenital lesions of the kidney or ureter.

WILLIAMSON, New Orleans.

INFANTILISM OF RENAL ORIGIN. L. ROWLEY, Proc. Roy. Soc. Med. **39**:588 (Aug.) 1946.

The patient, a boy 19 months old, had vomited after meals off and on since birth. He was an only child and was small for his age, his weight being one-half what it should have been. He had an insatiable thirst. Routine urinalysis showed

85 mg. of albumin per hundred cubic centimeters. The blood count, the blood biochemistry and the roentgenographic findings are given in the report. The blood urea was 96 mg. per hundred cubic centimeters; the first clearance test showed 26.1 per cent and the second, 21.6 per cent.

WILLIAMSON, New Orleans.

SUBACUTE NEPHRITIS. DONALD PATERSON, Proc. Roy. Soc. Med. **39**:593 (Aug.) 1946.

The patient, a boy aged 5½ years, had fever, abdominal pain and emesis with swelling of the right elbow and wrist and the right testis. On his admission to the hospital examination revealed edema of the face, purpuric spots on the arms and hematuria. By the Addis count, the urine for twenty-four hours contained 260 mg. of albumin, 2,200,000 red blood cells, 500,000 white cells and no casts, and the blood urea was 36 mg. per hundred cubic centimeters.

A month later the child became extremely ill. The heart was enlarged, and a loud systolic apical murmur was heard. A pleural effusion developed on the right side a short time later. Then gradual improvement was noticed, and the child was sent home, to remain in bed three months. At that time his general condition was good. The number of red and white cells in the urine had diminished, but many casts were observed. A roentgenogram of the chest revealed nothing pathologic. The blood pressure was 120 systolic and 80 diastolic.

WILLIAMSON, New Orleans.

(1) CHRONIC NEPHRITIS AND RENAL DWARFISM; (2) NEPHROSIS. DONALD PATERSON, Proc. Roy. Soc. Med. **39**:594 (Aug.) 1946.

The first case was that of a boy aged 7½ years; the case of nephrosis, that of a boy aged 4 years.

WILLIAMSON, New Orleans.

RENAL TUMOR WITH PECULIAR EXTENSION TO THE RIGHT AURICLE: REPORT OF A CASE. ARMANDO CARNEVALE, Pediatria **54**:127, 1946.

The author presents the case of adenosarcoma of the left kidney in a 9 year old girl with peculiar spread of the neoplasm into the ascendant vena cava and simultaneous diffusion into the right auricle. FROM THE AUTHOR'S ABSTRACT.

Diseases of the Ductless Glands; Endocrinology

LATE IMPROVEMENT IN A CASE OF CONGENITAL ATHYROID NANISM WITH ALTERATION OF THE SELLA TURCICA. F. BAMATTER, A. FRANCESCHETTI and D. KLEIN, Helvet. pædiat. acta **2**:154 (April) 1947.

A study is presented of a girl aged 13½ years, 81 cm. (31 inches) in height with myxidiocy. She came of a family of wandering cauldron and basket makers in central Switzerland, which contained multiple hereditary defects and in which there was already a case of phenylpyruvic dwarfism. The lack of physical and psychic development reduced the child to the status of a malformed suckling. Her bony development corresponded to that of the first months of extrauterine life. Other manifestations were: brachycephalic skull; depression of the bridge of the nose; calcification in the hypophysial region; increased tendon reflexes with a Babinski sign; normochromic anemia with relative lymphocytosis; erythropoietic aplasia and myelopoietic hypoplasia, as observed in the myelogram; hypercholesteremia, and reduction of the basal metabolic rate to minus 30 per cent.

The child was placed under treatment with a preparation of the thyroid gland and thyroxin. There was intolerance to therapy at first, then adaptation and progressive improvement. The final result was an increase in height from 81 to 93.5 cm. (31 to 37 inches) in one year. The centers of ossification developed to the 5 year stage. The myxedema disappeared, and the expression became more normal. The blood formula, but not the bone marrow count, became normal. The emotional behavior improved appreciably and there was some improvement in the intellectual functions.

The authors also discuss the hereditary factors in the case, with reference also to an observation on 2 brothers with hypothyroidism now in an asylum, who were the offspring of a marriage of first cousins. FROM THE AUTHORS' ABSTRACT.

Diseases of the Muscles, Bones, Joints and Lymph Glands

CONGENITAL ABSENCE OF PEDICLE FROM THE CERVICAL VERTEBRA: REPORT OF THREE CASES. LEE A. HADLEY, Am. J. Roentgenol. **55**:193 (Feb.) 1946.

The author enumerates various types of congenital anomalies of the cervical region. Absence of a pedicle may remain unrecognized unless roentgenologic study of the cervical region is initiated for some other reason. An enlargement of the intervertebral foramen is noticeable at the level of the defect. The condition does not seem painful. Visualization is best accomplished by the 45 degree oblique roentgenogram. Three cases are reported with histories and discussion, accompanied with roentgenograms and explanatory diagrams. HARRISON, Chicago.

LUECKENSCHAEDEL (LACUNA SKULL) IN A PATIENT WITH AMNESIA AMENABLE TO HYPNOTHERAPY: A PERSONALITY PROBLEM. JEROME M. SCHNECK, J. Nerv. & Ment. Dis. **104**:249 (Sept.) 1946.

The case reported is that of an 18 year old youth who, two days after entering the Army of the United States, became amnesic. An interesting review of the literature of "lacuna skull" is included in the article. JAHR, Omaha.

PROGRESSIVE OSSIFYING MYOSITIS: REPORT OF A CASE. ALDO DE BLASIO, Pediatria **55**:116 (Jan.-March) 1947.

After outlining the characteristics of the syndrome and the pathogenesis of progressive ossifying myositis as found in the literature, the author describes a case he observed. From the results obtained during various researches, he points out the peculiar behavior of Bufano's curve for the amino acids of the blood and the various elements favorable to the thesis of a basic thyroid dysfunction.

FROM THE AUTHOR'S ABSTRACT.

BILATERAL CONGENITAL MUSCULAR TORTICOLLIS. R. H. VON MURALT, Helvet. pædiat. acta **1**:349 (May) 1946.

The symptoms in a case of bilateral congenital muscular torticollis are described and compared with those in the few cases which have been published so far. Two of these cases prove the existence of forms of gradual transition. The frequent anatomic variations of the sternocleidomastoid muscle and the usual dominance of one side over the other probably constitute the reason that bilateral wryneck, as compared with other congenital malformations, is rarely recognized. Its bilateral occurrence is an important argument for the congenital origin of wryneck on the

basis of germinal dysplasia. The frequent coexistence of other congenital malformations favors this conception. That the ontogenetically related trapezius muscle is rarely affected might be explained by the theory of the dysmetameric origin of the sternocleidomastoid muscle. FROM THE AUTHOR'S ABSTRACT.

Skin Diseases; Allergy

EMOTIONS AND THE ALLERGIC INDIVIDUAL. FRANK C. METZGER, Am. J. Psychiat. **103**:697 (March) 1947.

Clinical experiments and personal experience led the author to the conclusion that there is a definite relation between emotional reaction and symptomatic attacks of allergy in many allergic patients. Attacks of asthma, urticaria and hay fever were produced in several patients on the basis of fear, suspicion and anger; relief was secured by suggestion or by the explanation of the experimental phases of these clinical experiments.

JAHR, Omaha.

HISTAMINE AZOPROTEIN IN THE TREATMENT OF ALLERGY. MILTON B. COHEN and HAROLD J. FREIDMAN, Allergy **18**:7 (Jan.) 1947.

Histamine azoprotein is of value in treatment of urticaria and in some cases of bronchial asthma but is of no value in the prevention of hay fever.

HOYER, Cincinnati.

CLINICAL AND SEROLOGIC STUDY OF RAGWEED HAY FEVER PATIENTS TREATED WITH HISTAMINE AZOPROTEIN (HAPAMINE): ABBREVIATED REPORT. SELIAN HEBALD, ROBERT A. COOKE and LILLIAN M. DOWNING, J. Allergy **18**:13 (Jan.) 1947.

"There appeared to be no clinical benefit resulting from treatment with histamine azoprotein."

HOYER, Cincinnati.

THE PATHOGENESIS OF INFANTILE ECZEMA: CRITICAL REVIEW. LEWIS WEBB HILL, J. Allergy **18**:60 (Jan.) 1947.

The author agrees with Cooke that the patch test gives valid etiologic information, but does not agree with his statement that the urticarial type of reaction as produced by a scratch or an intracutaneous test gives no information, since allergens which produce this reaction may produce urticaria or eczema, depending on many circumstances.

There is no fundamental difference in the patch, scratch and intracutaneous tests. The reaction in each is caused by irritation of blood vessels—in the patch test by mild irritation of superficial vessels responding slowly, and in the scratch and intracutaneous tests by irritation of deeper vessels, giving a response quickly and violently.

As a working hypothesis for the pathogenesis of infantile eczema, the following points are presented: The condition occurs usually in a child having an allergic background. Early in life he becomes sensitized to a strong sensitizer, such as egg white, fish or nuts; this may occur in utero or through breast milk. The primary sensitization paves the way for secondary sensitization to foods, such as wheat, and to environmental allergens, such as dust, feathers, ragweed and hair dander.

Unsplit food protein has to be absorbed at some time to produce a positive reaction to a cutaneous test. No damage to the skin will occur if no protein is

absorbed from the corresponding food even though the reaction to the cutaneous test is positive. The eczematous response originates in the small papillary vessels below the epidermis.

HOYER, Cincinnati.

PENICILLIN IN INTRACTABLE ASTHMA. MALCOLM W. MILLER, J. Allergy **18**:109 (March) 1947.

The literature concerning the use of penicillin in treatment of intrinsic asthma was reviewed and 29 additional cases were reported in which penicillin was administered intramuscularly.

The author concludes that penicillin cannot be considered a panacea for intractable asthma. It should be regarded as an agent for the treatment of infectious processes. As such, it is effective in a small proportion of selected cases. The results warrant further study of the use of penicillin in cases of intrinsic asthma.

HOYER, Cincinnati.

EFFECTIVE TREATMENT OF EXTREMELY SENSITIVE HAY FEVER PATIENTS BY THE CILLING METHOD. LEOPOLD C. LAZAROWITZ, J. Allergy **18**:104 (March) 1947.

To retard the circulation in and around the site of the injection, a small ice bag was supported by a bandage to the midouter part of the arm for fifteen minutes prior to and for fifteen minutes after a subcutaneous injection of ragweed extract.

This procedure made it possible to give larger doses of vaccine; it cut down the number of visits, and it rendered the injections painless. Constitutional reaction occurred seldom, and no delayed reaction was observed.

HOYER, Cincinnati.

THE ACTION OF HISTAMINE ON THE RESPIRATORY TRACT IN NORMAL AND ASTHMATIC SUBJECTS. JOHN J. CURRY, J. Clin. Investigation **25**:785 (Nov.) 1946.

Histamine was administered to three groups of subjects in whom the degree of bronchoconstriction was assayed by measurements of the vital capacity. The first group comprised 10 normal subjects; the second, 10 patients with severe allergic tendencies, including asthma, and the third, 9 patients with varying degrees of chronic bronchitis, emphysema and asthma.

No significant decrease in vital capacity was observed in the first two groups after histamine was administered intramuscularly or intravenously. Five patients with a history of asthma showed no significant bronchoconstriction after injection of histamine. However, 8 of the 9 patients with active asthma and varying degrees of bronchitis and emphysema did show sensitivity of the tracheobronchial tree to histamine. This sensitivity varied in the different patients, and varied in the same person with the degree of asthma.

Gradually increasing doses of histamine produced greater bronchoconstriction, while gradually decreasing doses had the reverse effect. In any one period, the decreases in vital capacity produced by identical amounts of histamine, regardless of the order of dosage, were similar and ruled out any cumulative effect. Bronchoconstriction was also induced with histamine given sublingually and by nebulization.

Systemic reactions to histamine (flush and headache) appeared no severer in asthmatic than in normal subjects.

BRODSKY, Cincinnati.

THE EFFECT OF ANTIHISTAMINE SUBSTANCES AND OTHER DRUGS ON HISTAMINE BRONCHOCONSTRICTION IN ASTHMATIC PATIENTS. JOHN J. CURRY, J. Clin. Investigation **25**:792 (Nov.) 1946.

The ability of certain antihistamine substances, sympathomimetic amines and other drugs to counteract bronchoconstriction due to histamine was studied. The degree of bronchoconstriction was measured by recording the decreases in vital capacity. Asthmatic patients previously found to be sensitive to histamine were used in this study.

Diphenhydramine hydrochloride ("benadryl hydrochloride") given intravenously in doses of from 10 to 30 mg. effectively prevented the fall in vital capacity after administration of 0.02 mg. of histamine. This protection lasted from two minutes to two hours after administration of diphenhydramine hydrochloride. The drug also protected against systemic effects of histamine. Pyribenzamine hydrochloride (N'-pyridyl-N'-benzyl-N-dimethylethylenediamine monohydrochloride) given orally in doses of 50 mg. exerted a slower and more irregular protection.

Atropine sulfate completely counteracted the bronchoconstrictive action of nebulized histamine in 1 case, but afforded only partial protection against intravenously administered histamine.

Aminophylline given intravenously provided prompt and potent protection against the bronchoconstrictive action of intravenously administered histamine.

Intramuscular administration of epinephrine and ephedrine gave prompt and complete protection against the bronchoconstrictive effects of histamine. However, protection of ephedrine was slow, becoming complete only two hours after administration.

The authors suggest that the measurement of vital capacity be used as a means of assaying the bronchodilator activity of various sympathomimetic amines.

BRODSKY, Cincinnati.

Miscellaneous

STUDIES ON THE PHARMACOLOGY OF DDT [4-4'-(DICHLORODIPHENYLTRICHLOROETHANE)]: 1. THE ACUTE TOXICITY OF DDT FOLLOWING INTRAVENOUS INJECTION IN MAMMALS WITH OBSERVATIONS ON THE TREATMENT OF ACUTE DDT POISONING. FREDERICK S. PHILIPS and ALFRED GILMAN, J. Pharmacol. & Exper. Therap. **86**:213 (March) 1946.

DDT (dichlorodiphenyltrichloroethane) caused tremors leading to convulsions and, with large doses, to death in experimental animals. Death may be due either to exhaustion from the convulsions or to ventricular fibrillation (more common in dogs). The most effective remedy against the action of DDT was phenobarbital in doses that caused a minimal degree of general depression in the central nervous system. With more toxic doses of the drug full anesthetic action of phenobarbital was required. With excessive doses of the poison the antidote was not effective.

PILCHER, Cleveland.

BEHAVIOR OF SYNTHETIC ESTERS OF STROPHANTHIDIN, THE ACETATE, PROPIONATE, BUTYRATE, AND BENZOATE, IN MAN. HARRY GOLD, HAROLD L. OTTO, WALTER MODELL and SEYMOUR L. HALPERN, J. Pharmacol. & Exper. Therap. **86**:301 (March) 1946.

Study was made of 1,500 patients with cardiac disease associated with auricular fibrillation and heart failure. The results show that the esters of K-strophanthidin

act similarly to digitalis in man; that is, they slow the ventricular rate in cases of auricular fibrillation, produce nausea and vomiting both by systemic and by local action in the gastrointestinal tract and probably exert a similar effect on the symptoms of heart failure. The acetate and propionate are poorly absorbed from the gastrointestinal tract; the butyrate is absorbed rapidly when administered by mouth, producing its full effect in an hour; the benzoate is very rapidly absorbed, approaching the absorption of digitoxin.

PILCHER, Cleveland

ON MALIGNANT NEWGROWTH IN FILIPINO CHILDREN. EUGENE STRANSKY and LEON V. PECACHE, Ann. pædiat. **166**:139 (March) 1946.

In the Philippine General Hospital 19 cases of cancer in childhood were collected during a period of four and one-half years, from June 1939 until December 1943. Two were cases of carcinoma, one a primary hepatic carcinoma with metastases to the lungs, the bones and the lymph nodes, and the other a metastatic carcinoma of the cervical and mediastinal lymph nodes, with the thyroid as the probable site of the primary tumor. Of the 19 cases 5 were lymphosarcoma, 3 of which started as mesenteric, 1 as cecal and 1 as mediastinal tumor. The importance of the presence of chylous exudate in these particular cases is emphasized. Three cases of Hodgkin's disease are discussed. One of them showed the signs and symptoms of Brill-Symmer disease or follicular lymphoblastoma, which soon developed into Hodgkin's granuloma. This is the first case of this rare condition observed and diagnosed in the Philippines. The second case started in an intra-abdominal lymph node, while the third case originated from the cervical lymph nodes, as the majority of the cases do, to spread later to the different organs thus showing the symptoms of infiltrating growth, hence a Hodgkin's sarcoma. There are autopsy and histologic reports of the case of primary hepatic carcinoma, of 3 cases of lymphosarcoma and of the case of Hodgkin's sarcoma. Nine cases of embryonic malignant neoplasm are reported with the following varieties: 2 cases of adrenal neuroblastoma (sympathicoblastoma), 1 of them with a complete anatomic and histologic report, the second with biopsy reports; 3 cases of retinoblastoma (the former term is retinal glioma), for 1 case of which there is a necropsy report, for the second a report of operation and a histologic report and for the third a report of aspiration biopsy and of symptoms of metastases. Three cases of embryonal carcinosarcoma of the kidney are presented, 2 with an autopsy report and 1 with operative and histologic confirmation. One case of hypernephroma with operative and histologic report is also included.

There are detailed clinical and anatomic reports including symptoms of important cases, aside from a short summary of all 19 cases.

Sixteen of the 19 patients were males and only 3 females.

AUTHORS' SUMMARY.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Joseph Greengard, M.D., *President*
Regular Meeting, Jan. 21, 1947

Syndromes of Kerosene Poisoning in Children. Dr. Matthew M. Steiner.

Cases of kerosene poisoning in children were divided into three main groups on the basis of severity and complications. Group 1 comprised 26 cases characterized by signs of acute intoxication with depression of the central nervous system, minimal pulmonary signs and rapid recovery. Group 2 comprised 6 cases in which there developed severe pneumonia and hyperpyrexia, with prolonged recovery and convalescence. Group 3 consisted of 4 cases in which there developed severe pneumonia and degenerative changes in the heart, liver, spleen and gastrointestinal tract. A complication in these cases hitherto not encountered with kerosene poisoning was that of auricular fibrillation and flutter. The changes in the gastrointestinal tract as a result of direct contact with the kerosene were evidenced by the presence of blood in the vomitus and stools.

Emergency treatment consisted in gastric lavage with copious amounts of weak solution of sodium bicarbonate for the removal of the kerosene and prevention of further absorption by and damage to the gastrointestinal mucosa. Nikethamide and/or caffeine were employed when such stimulants seemed indicated by the condition of the patient. Penicillin therapy was instituted early in the cases of more serious poisoning to offset bacterial invasion of the lungs. Intravenous administration of hypertonic (50 per cent) solution of dextrose, as well as use of the oxygen tent, appeared efficacious in diminishing the hazard of early pulmonary edema in the serious cases. Adequate intake of fluids and electrolytes was maintained by parenteral administration, especially in those critically ill patients with severe pneumonia or degenerative changes in various organs. Digitalis was employed when indicated.

DISCUSSION

Dr. William D. McNally: There can be little discussion on this paper because Dr. Steiner has covered practically every phase of the treatment and the pathologic changes. I have some data which may be of interest. At Cook County Hospital there have been no deaths from kerosene poisoning because of the efficient staff, but some do occur outside the hospital. Nearly every case of kerosene poisoning occurs in cold weather; poor families use oil burners for heating, and, of course, there are more fires in cold weather. Fortunately, when a child does drink kerosene, he gets only a small amount; specimens of stomach washings usually show only a trace. Whether the child has taken fuel oil or kerosene, the treatment is that outlined by Dr. Steiner.

There is little in the literature on this subject. Some authors do not favor washing out the stomach, but I believe this should be done. The child is in shock, and this condition must be treated with nikethamide or caffeine or any means that is effective. For edema I would suggest a mercurial diuretic, which is excellent for reducing edema of the lungs. I also administer "salyrgen" (mersalyl) and put the child into an oxygen tent. Results of this treatment are good. There is no

specific treatment for kerosene poisoning, as there is for chemical poisoning. Therefore, washing out the stomach with a solution of sodium bicarbonate is recommended.

The incidence of cases of fuel oil poisoning in Cook County Hospital, 43 in all from 1941 to 1946, ran as follows:

Year	No. of Cases
1941	10
1942	6
1943	2
1944	3
1945	8
1946	14

DR. GERARD N. KROST: Is there any objection to the use of a purge? My associates and I had a case at Wesley Memorial Hospital in which the child passed kerosene the next day and one could smell it in the stool.

DR. MATTHEW M. STEINER: In reply to Dr. Krost, it has been recommended that high colonic irrigation or enemas be used. If a patient is seen after some kerosene has passed through the stomach, it might be wise to hasten the passage of kerosene in that way.

Familial Incidence of Rheumatic Heart Disease. DR. WERNER K. GOTTSTEIN.

Modern investigation has confirmed the concept of Austin Flint that the constitutional predisposition is an essential etiologic factor in rheumatic fever. Further research will have to explain the causes of this congenital and familial susceptibility. The pathologic and biochemical changes in the connective tissue deserve special attention, as this tissue is the site of predilection of rheumatic fever. Structural anomalies and biochemical dysfunction of the mesodermal connective tissue are induced in embryonic life and are determined by the ectoderm.

A description was given of three generations of a family with multiple ectodermal and mesodermal anomalies associated with a familial occurrence of rheumatic fever. Additional observations confirmed the concept of a relation between structural anomalies and a tendency to rheumatic disease. It was concluded that the history and examination of children with rheumatic fever should be concerned with the following associations: (1) ectodermal anomalies of the patient and his relatives; (2) mesodermal aberrations, particularly a familial predisposition to disease of the coronary arteries or peripheral vascular disorders and the coincidence of rheumatic and congenital heart disease, and (3) congenital metabolic diseases. Disturbances in metabolism of the sulfur-rich protein compounds and congenital allergy are possibly involved in the constitutional predisposition.

Improved knowledge concerning the constitutional etiologic factors should not weaken one's efforts in the battle against poverty and infection, the enemies from without.

DISCUSSION

DR. ETHEL M. DAVIS: I have been interested in Dr. Gottstein's excellent presentation, for he considered several of the problems which my associates and I have been studying for a long time. Those of us who have studied large numbers of children with rheumatic heart disease have been struck with a similarity in the incidences of heart disease, rheumatic fever and cardiac manifestations in the same family. In a group of 110 rheumatic children studied from the epidemiologic standpoint, 35, or 32 per cent, presented evidence of a familial incidence.

One of Dr. Gottstein's most interesting points was his suggestion that the pathologic changes in rheumatic fever are based on a hypersensitivity. The etiologic factor in rheumatic fever is, of course, unknown. It has been postulated that the manifestations of rheumatic fever have as their basis a hypersensitive reaction to infective micro-organisms rather than actual tissue involvement of the heart itself by the organism. Dr. Gottstein spoke of the incidence of allergic manifestations, hay fever and asthma in certain cases of rheumatic fever. That these allergic disturbances have a similar familial tendency is an intriguing idea.

One must remember that over 10 per cent of the general population show evidence of the major allergic disturbances, such as asthma or hay fever. If the manifestations of rheumatic fever are on an allergic basis, the mechanism is of a different type than that involved in ordinary allergic (atopic) manifestations; for in the latter the pathologic process is entirely reversible. In rheumatic fever and other similar manifestations there is actual tissue damage, as evidenced by necrosis of the connective and elastic tissues. If the reaction is one of hypersensitivity, it probably has a mechanism different from that of atopic phenomena, one which may be similar to that of the Shwartzman, or even the Arthus, phenomenon.

DR. ARTHUR H. ROSENBLUM: Dr. Gottstein has opened a new approach to this problem. A few years ago, at the suggestion of Dr. Philip Rosenblum, Ruth Rosenblum and I studied a series of 70 families with rheumatic fever. We studied these families in their homes and examined all available members, rather than rely on histories, which are frequently misleading. We found a decided familial trend. In 40 per cent of the families additional members with the disease were found among siblings or parents. In the families in which one or both parents were rheumatic, the incidence of the condition in the siblings was almost doubled. Congenital heart disease was also seen not infrequently in these families, and there were a few persons who apparently had the combined lesions of congenital and rheumatic heart disease.

DR. WERNER K. GOTTSTEIN: I believe it is of great importance not to overemphasize the endogenous susceptibility, but to stress the exogenous factors, in treatment such as nutrition and use of the sulfonamide drugs. Especially important is the influence of climate. One is inclined to recommend that the child be taken to Arizona or Florida without asking who is to pay for it. If one is to burden the parents in this way, one should be sure the child will be benefited. It has been thought that rheumatic fever is not so prevalent in the South as elsewhere, but medical statistics are poor in many parts of this region. During the war many reports showed that the disease occurs frequently there. In my opinion, the problem should be reviewed.

The place of allergic hypersensitivity in the causation of rheumatic fever is difficult to evaluate. The last word has not been spoken. The fact remains that rheumatic fever is a systemic disease of the connective tissue. Familial and congenital factors must play a role in making the tissue more susceptible to damage.

The study of familial diseases is difficult. It is easier to raise drosophilas in pint bottles than to collect modest, but incontestable, data on human pedigrees. Often one learns from the history of an interesting associated anomaly in a member of the family, but a check of the records in various hospitals does not verify the information. Some patients with rheumatic fever go from hospital to hospital; I know of a child who went from St. Luke's to Jackson Park Hospital and is now at Mount Sinai Hospital. It is difficult to study family problems, but pediatrics has developed out of the experiences of family physicians. One can understand the sick child, physically and mentally, only by considering the hereditary and environmental family problems. I hope that my talk has contributed a little in this direction.

Book Reviews

Tutoring as Therapy. By Grace Arthur, Ph.D. Price, $1.50. Pp. 125, with no illustrations. New York: The Commonwealth Fund, 1946.

The author of this book is a clinical psychologist of wide experience. She is the author of the "Point Scale of Performance Tests."

Dr. Arthur gives an excellent description of her experience in remedial teaching in the public schools of St. Paul, Minn. She stresses the need of careful psychologic diagnosis before tutoring is undertaken, and of terminating such therapy at the optimum time. One chapter is devoted to the selection, training and supervision of tutors for a large project serving an entire school system, such as the one under her supervision.

The book is well seasoned by many illustrative case reports, and merits the interest of pediatricians who are increasingly aware of the many specific learning difficulties existing among their patients.

Dr. Arthur closes with a plea for the cooperation of all professional groups dealing with children in the establishment of a tutoring project as a community undertaking.

Differential Diagnosis of Jaundice. L. Schiff, M.D. Price, $5.50. Pp. 302. Chicago: Year Book Publishers, Inc., 1946.

As the title indicates, this book is a clinical discussion of the subject of jaundice. jaundice and retention jaundice. In keeping with the extensive recent literature on jaundice, and retention jaundice. In keeping with the extensive recent literature on various forms of infectious hepatitis, this subject is covered in considerable detail. A special chapter on jaundice of the neonatal period by Samuel Rapoport has been included. A final section on clinical and laboratory aids in differential diagnosis of jaundice is most useful. The latest laboratory methods are described in detail.

This book is a strictly up-to-date, practical, concise and reasonably complete discussion of a subject in which radical changes have occurred in recent years. It should prove valuable to specialists as well as general practitioners.

Pointers for Parents. Reinhard V. Lozier, M.D. Price, $2. Pp. 141. Philadelphia: J. B. Lippincott Company, 1947.

This little book, written for the laity, is divided into fifteen chapters, which cover the years from infancy into marriage. No one phase or problem in development is covered thoroughly. The instructions are didactic, and each chapter is summarized with do's and don'ts. Nothing new is offered.

A rigid schedule from the beginning is emphasized. The controversial issue of self demand in infant feeding is not mentioned. There is an apparent lack of understanding of growth and development of the infant and small child, including an occasional error.

The book is safe. It is written in a crisp unscholarly style and contains many cleverly informative sketches. In a discipline-needed world, its propaganda would reach and help the busy mother with her child of 2 years or older. The new mother with a small infant needs more than this book offers.

Diabetic Care in Pictures. Helen Rosenthal, Frances Stern and Joseph Rosenthal. Price, $2.00. Pp. 150, with 137 illustrations. Philadelphia: J. B. Lippincott Company, 1946.

This is an excellent teaching manual recommended especially for children and their families, patients whose background is not adequate for the usual manual and for those with language difficulties. All diabetic patients will find the manual profitable, especially the dietary chapters.

Also to be recommended are the pictures and explanations of the different types of syringes and insulins.

Emergency situations are anticipated and all essentials are given simply, with care not to confuse or frighten the patient.

Psychiatric Interviews with Children. Helen Leland Witmer, Editor. Price, $4.50. Pp. 443. New York: Commonwealth Fund, 1947.

This book of records of psychiatric treatment of children gives a complete concrete picture of present day child psychiatry. Detailed case records of eight qualified child psychiatrists give a clinical picture of therapeutic procedures. There are careful descriptions of the behavior of the children treated and the psychiatrist's interpretation of their behavior, as well as his attitude toward his patients during interviews.

The first case describes the play therapy of a boy who required foster home care, but who did not show signs of abnormal or neurotic behavior. The author points out the reason for considering the patient normal. The second case was that of a child with a reading problem, on a psychologic basis. Subsequent cases deal with children who displayed neurotic or other behavior requiring psychiatric care.

The cases were selected by the author from various clinics. In addition to the discussions of each case, there is a description of the principles of psychotherapy and their method of appreciation. This book was written for students and others concerned with child welfare. It is an extremely interesting and valuable addition to current literature.

Psychotherapy in Medical Practice. By Maurice Levine, M.D. Price, $3.50. Pp. 320, with no charts or illustrations. New York: The Macmillan Company, 1946.

The author, formerly an internist and now a practicing neuropsychiatrist and psychoanalyst, has written this book for the general practitioner in order to aid him in treating patients with psychiatric diseases that he can safely manage. The book also attempts to describe those patients who would profit most by being referred to a specialist.

Devoid of psychiatric nomenclature there is a detailed description of "the methods for the practitioner," "advanced methods of the practitioner" and "methods for the specialist." The methods for the practitioner are similar to those used by trained social service workers.

Chapters are devoted to suicidal risks, a classification of abnormal mental states, sex and marriage, basic attitudes toward children and the problems of parents and children. There is a final chapter on suggestions for further reading.

This book is an outstanding effort to meet the need of those physicians who are not trained in psychiatry. It is well written in an interesting, understandable style.